#37 Revive 4/11/03

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Gordon et al.
Serial No. : 07/839,194
Filed : February 20, 1992
Title : TRANSGENIC ANIMALS SECRETING DESIRED PROTEINS INTO MILK

Art Unit : 1632
Examiner : Debra Crouch

BOX AF
Commissioner for Patents
Washington, D.C. 20231

BRIEF ON APPEAL

This Appeal Brief is being filed in response to the office action dated January 30, 2001 and the Notice of Appeal filed on September 6, 2001. The period of time for filing an appeal brief was set by the Petition to Revive mailed on August 22, 2002.

(1) Real Party in Interest

The Real Party in Interest is GTC BioTherapeutics, 175 Crossing Blvd., Framingham, Massachusetts 01701, that has an exclusive license from the assignee, Genzyme Corporation, One Mountain Road, Framingham, Massachusetts, 01701.

(2) Related Appeals and Interferences

This application is a divisional of U.S. Serial Number 07/441,785 (abandoned), which is a divisional of U.S. Serial Number 06/849,815 (abandoned). An appeal brief has been filed in U.S. Serial Number 07/938,322, which is related to the above-identified application. Specifically, U.S. Serial Number 07/938,322 is a continuation of U.S. Serial Number 07/426,464 (abandoned), which is a continuation of U.S. Serial Number 07/109,922 (abandoned), which is a divisional of U.S. Serial Number 06/849,815 (abandoned). We received notice from the U.S. Patent & Trademark Office on August 14, 2002, that U.S. Serial Number 07/938,322 has been forwarded to the Board of Patent Appeals and Interferences for a decision.

(3) Status of Claims

Claims 1, 2, 5-9, 11, 16, 17, 19-22 and 24-29 are pending.

Claims 1, 2, 5-9, 11, 16, 17, 19-22 and 24-29 have been rejected under 35 U.S.C. §112, first paragraph.

Claims 1, 5-9, 11, 16, 17, 19-22 and 24-29 have been provisionally rejected under 35 U.S.C. §101 for statutory double patenting over 08/927,936.

Claim 2 has been provisionally rejected under the judicially created doctrine of obvious-type double patenting as being unpatentable over 08/927,936 and claims 1, 2, 5-9, 11, 16, 19-21 and 24-29 as being unpatentable over 08/246,259

(4) Status of Amendments

All of the amendments filed in this case have been entered. Appellant notes that the claims will be argued or a terminal disclaimer will be filed to overcome the provisional rejection of the claims under the doctrine of obvious-type double patenting upon notification of allowance of any of the claims in this or the other pending applications. Appellant also notes that U.S. Serial Number 08/927,936 has been abandoned, thereby obviating any double patenting rejections with regard to that application. As such, these rejections are not addressed in this brief.

(5) Summary of Invention

The invention relates to a DNA construct. The DNA construct includes a gene encoding a protein. The coding sequence is under the transcriptional control of DNA derived from the 5' flanking region of a gene which encodes a protein which is specifically expressed in milk, in other words DNA which includes a mammalian milk protein promoter sequence that does not naturally control transcription of the gene. The DNA construct also includes DNA encoding a peptide which enables secretion of the protein into the milk.

The gene is under control of a sequence upstream from the transcriptional start site of a mammalian milk protein which includes a milk protein promoter. The milk protein can be a milk serum protein such as α-lactalbumin.

The peptide which enables secretion of the protein can be a signal peptide naturally associated with the gene encoding the protein or a signal peptide naturally associated with a milk protein. The signal peptide can be cleaved from the protein after secretion into the milk.

Examples of proteins which can be produced include human tissue plasminogen activator and hepatitis B surface antigen.

The DNA construct can also include a transcriptional stop sequence such as a stop sequence derived from SV40 viral DNA or a signal stop sequence contained within the polyadenylation sequence of SV40.

(6) Issue

Is there sufficient written description in the application under 35 U.S.C. §112, first paragraph for the subject matter of claims 1, 2, 5-9, 11, 16, 17, 19-22 and 24-29?

(7) Grouping of Claims

Appellant requests that the claims be considered in the following groups, the claims in each group standing or falling together:

I. Claims 1, 2, 5, 6, 7, 8, 9, and 11;

II. Claims 19, 20, 24, 25 and 29;

III. Claims 16, 26, 27 and 28;

IV. Claim 21;

V. Claim 17; and

VI. Claim 22.

Since the remaining rejection is based on written description, the claims have been grouped depending on whether a genus, subgenus or species of a milk protein promoter is recited in the claim. Therefore, the claims in each group listed above should stand or fall together.

(8) Argument

I. Summary of the Response to the Written Description Rejection

This summary is merely to orient the reader. Appellant's arguments, including a detailed discussion of the PTO Guidelines on written description and the case law as applied to the instant facts, and a detailed reply to the Examiner's rejections and comments, are provided in the full text below.

The invention in the instant application is a combination of three elements which were each, in isolation, know in the art. It is a vector which includes: (1) a region of DNA which includes a milk protein promoter, (2) a signal sequence, and (3) a nucleic acid encoding a protein other than

the protein normally associated with the milk protein promoter, (sometimes referred to herein as a heterologous gene or protein).

The rejections are all concerned with the first recited element, which includes a milk specific promoter. The claims have been rejected on the grounds that the written description of milk specific promoters is not sufficient. In other words, it was argued in the rejection that the text of the specification, together with what was known in the art, does not show that the inventors were in possession of the invention.

The rejection is improper. A number of fundamental flaws are interwoven in the Examiner's analysis and rejection. The principle errors are as follows.

Throughout her analysis, the Examiner has refused to evaluate the sufficiency of the written description provided in the specification in light of the skill and knowledge of the art, as is required by the case law and summarized in the PTO Guidelines on written description. If one heeds the analytical requirements set out in the Guidelines and case law, it is quite clear that, under the present facts, including the high level of skill and knowledge one of ordinary skill would bring to the specification, simply reciting the name of the milk specific promoter regions (as is done in the specification) is a sufficient written description.

A second major flaw runs throughout the Examiner's analysis, namely the Examiner's refusal to analyze and apply the requirements for written description to the actual claims, as they appear in the instant application. The Examiner's analysis ignores the fact that the claim element at issue is simply a sequence or region which includes a milk specific promoter. The claims do not claim any special motif and no knowledge of such a motif (if it even exists and even if it is within the claimed promoter region) is required to select milk specific promoters. Specifically, as is discussed below, no such motif or knowledge of such motif is required to identify or distinguish milk specific promoter regions from other promoters.

A third and related flaw in the Examiner's analysis also based in the Examiner's view of the centrality of a motif which is unique to milk specific promoters. The Examiner has formulated a particular technical landmark, namely the identification of specific motifs within the milk specific promoter regions that are characteristic of milk specific promoters. The Examiner demands that these be described. The elucidation of such motifs might well be one way of describing milk specific promoters. The critical issue is not whether they would or would not. The critical issue is that the Examiner ignores other information which provide entirely different, and entirely sufficient ways, of identifying milk specific promoter regions and distinguishing them from other promoters in terms of their functional and physiological role. The Examiner concentrates solely on a way she has come up with to provide a description and has ignored another wholly sufficient way provided by the art.

Finally, the Examiner has misapplied the teachings of the relevant case law.

Any one of these errors alone is sufficient to vitiate the Examiner's position. These, and others errors in the Examiner's analysis are discussed in more detail below.

The specification recites milk specific promoters and names two types of milk specific promoter, WAP and α-lactalbumin, and one sub-genus of milk specific promoters, namely the caseins. The specification recites considerable detail for one of the promoters, the WAP promoter. The level of detail for the WAP promoter does not differ significantly from the level of detail known in the art for the other recited promoter or for the promoters of the casein sub-genus. (Thus, the Examiner's conclusion with respect to WAP actually requires a finding that the other promoters are adequately described.)

We turn now to one of the fatal flaws that runs throughout the Examiner's arguments, namely the Examiner's refusal to evaluate the sufficiency of the written description provided in the specification in light of the skill and knowledge of the art. Milk specific promoter regions or sequences were extremely well known in the art at the time of filing. The promoter regions were sufficiently well known that merely naming them would put one in possession of them as an element of the claimed invention. The extensive characterization, including the occurrence and position of canonical promoter structures[1] and the structural linkage of the promoter regions in question to genes which encode milk specific proteins, allowed one of ordinary skill in the art, when armed with the knowledge of the art, and the specification, to distinguish milk specific promoters from other promoters. E.g., skin specific promoters which, while they may include canonical structures, differ structurally from milk specific promoter regions in that they are structurally linked to coding regions for skin specific proteins, as opposed to genes which encode milk specific proteins. The canonical structures tells one that it is a promoter and being part of the structure of a gene which encodes a milk specific protein tells one that it is a milk specific promoter, and not, e.g., a skin specific or liver specific promoter which are tied to the production of certain proteins upon specific expression events in the skin or liver.

In other words, the identifying characteristic provided by the Appellant for a sequence or region which includes a milk specific promoter is simply the name of the promoter. Naming is sufficient, given the fact that these promoter regions were already known in the art. Naming is sufficient in that it clearly conveys what was invented--the "essential goal" of the written description requirement. (It is important to remain focused on the invention, which is the combination of a milk specific promoter sequence or region (and those terms, sequence and region, are equivalent as used in the claims) with other known elements to produce a combination that is new.) By pointing to the promoter region by naming, when the promoter

[1] As used herein the term canonical or generic refers to promoter structures present in all or most promoters, including milk specific promoters,

region is structurally and physically characterized in the art, the Appellant is saying "use this specific structurally characterized art-known element." The degree of detail needed to convey the realization that the inventor was in possession depends on the essential character of the invention and the level of skill and knowledge in the art. If the art were devoid of information as to milk specific genes and promoters, a great level of detail might be called for. However, in this case the level of knowledge and skill in the art was considerable and naming of the known element was sufficient.

As will be described in more detail below, see, e.g., section II.3, an analysis of the sufficiency of a written description cannot be made in an isolated or purely abstract sense. Rather, the case law and the Guidelines require that the inquiry must be made from the standpoint of one imbued with the skill and knowledge of the art. The disclosure must place one in possession of the invention, but the case law and the Guidelines provide explicitly that the greater the level of skill and knowledge in the art, the less specificity a disclosure needs to provide. Information well known in the art need not be described in detail in the specification. The knowledge and skill in the art with regard to identity and structure of the small genus (there are about 7 types of milk specific proteins, so there are about 7 types of milk specific promoters) of milk promoters was very well developed—there was no need to include minute detail to convey possession of the invention. In the sections which follow, see e.g., section II.3.i-ii, the Appellant will discuss two types of references which show the development of the art. The level of skill in the art is shown below for a first class of references which disclose DNA fragments which include the very milk specific promoters argued by the Examiner to not be described.

In this regard, Appellant points to the five references (all published prior to the filing date of the instant application) discussed below in sections II.3.i. These references provide the cloned genomic sequence, identify the 3' end of the 5' regulatory region, identify characteristic 5' regulatory structures, and provide a significant amount of DNA sequence for the promoter regions, for examples of each of five of the seven types of milk promoters. This information, together with the specification, also teaches that one should look to genes which encode milk specific proteins to find milk specific promoter regions, which certainly goes a long way in helping one distinguish milk specific promoter regions from other promoter regions, e.g., those which are part of the structure of liver specific or skin specific genes (which are of course part of the structure of genes which encode liver or skin specific proteins). The disclosure of the references is summarized in Table 1 below.

The level of skill in the art is also shown by a second class or group of references which show the high degree of sophistication of the art with regard to the selection of elements and the combining of such elements into a single sequence in a vector. This latter class of references is not provided to in any way to try to focus on enablement and distract from the issue of written description but rather to help place the disclosure of the first group of references in context, to help illustrate what those references and the terms used in the specification would mean to one

who reads them. It is against this background of familiarity with the promoters that the sufficiency of the written description of the specification must be judged.

The art identifies a range of genes that encode mammary specific expression of proteins and it identifies the promoter regions associated with these genes. The promoters of mammary specific proteins are described in the art. Naming them is sufficient to show possession of the invention, which is a vector which includes a milk specific promoter region.

We turn now to another flaw in the rejection related to the Examiner's focus on motifs which are unique to milk specific promoters.

The disputed claim element is a DNA sequence having within it a milk specific promoter. The specification provides a written description of that claim element. The Guidelines and the case law require that analysis of the sufficiency of written description begin with the claims. The Examiner's analysis of the sufficiency of the written description has not been made with regard to the claimed invention. The claims require a sequence, and as used in the claims that means a region of nucleic acid which includes a milk specific promoter. The written description rejection hinges on the Examiner's requirement that the applicant should be forced to go beyond the claimed invention and provide a written description of something that is not claimed or needed to practice the claims. The Examiner demands that the inventors correlate the specific motifs within the promoter region that are responsible for mammary specific production in order to claim a vector which includes a region having a mammary specific promoter. The Examiner is of the view that the written description requirement is not satisfied by all of the art-known information on the milk specific promoters, including structural information such as extensive nucleic acid sequencing, the existence in the art of specific nucleic acids containing the promoters, and importantly, and never acknowledged by the Examiner, the fact that the promoter regions are found in nature controlling milk specific proteins. The Examiner goes beyond this and demands that the Appellant must also provide additional information about the special or unique sequence motif within the promoter that results in milk specific expression in order to provide a written description of the milk promoters.

This additional requirement imposed by the Examiner goes far beyond what is required by the law and ignores the actual claims. One can distinguish a milk specific promoter region from other promoter regions by the fact that canonical elements are present and by the fact that it is in a gene which encodes a milk specific protein. Milk specific proteins, and their genes, are a distinct and well characterized group of proteins (and genes). One can look to these promoters, known in the art to have, in nature as their native setting, this milk specific expression. The Examiner's demand for a correlation of internal motif believed to exist with activity is improper, unjust and goes beyond existing patent laws and established legal precedent.

The Examiner has looked beyond the claimed invention, which makes no mention of and does not rely on the identification of milk specific motifs, and proposed a further scientific exercise, and demanded a written description for that further exercise. What is the further exercise? It is a scientific inquiry which is in essence a more detailed fine structure analysis of promoter structure which correlates particular structures or motifs (structures the Examiner clearly believes to be within the claimed region) with the relevant biological activity, namely, mammary specificity. That sort of analysis may well be the next step an astute academic scientist would take in a purely scientific study of milk specific promoters. It might well be useful and provide additional, and even patentable, subject matter. But despite the potential value of such an investigation, it is simply not needed to provide a written description of the currently claimed element. That written description is provided by the specification when viewed in the light of the skill and knowledge of the art. If the invention were directed to the specific motif or structure responsible for mammary specificity, the level of description the Examiner is demanding might be required. But, that is not the instant invention and it is not the level of detail required to describe the instant invention.

If there were no other way of identifying and distinguishing milk specific promoters, the rejection might be justified, but as is described herein, the promoter regions can be and were identified by other means.

To adopt the Examiner's standard for written description would depart radically from the Guidelines and the case law. One might just as well extend the Examiner's standard to many of the other terms used in the claims, namely "a DNA construct", "a gene encoding a protein", "DNA encoding a peptide enabling secretion". None of these terms meet the Examiner's extraordinarily high (and incorrect) standard for written description but all do, like the milk specific promoter limitation, meet the requirements set out in the case law and the Guidelines.

In addition, even by the improperly high standards of the rejection, the written description is sufficient. Appellant disagrees with the Examiner's assertion that "none of the references provided by the Appellants identify any sequence or structure within the 5' flanking region for genes encoding α-lactalbumin, β-casein, and γ-casein that impart mammary gland specific expression." As is discussed below in section II.3.i, the elucidation of special motifs for many of the milk specific promoters the Examiner finds to be insufficiently described in the art is in fact described in the cited milk specific promoter references.

The inventors showed that the promoters can provide mammary specific expression in a transgenic animal of a heterologous protein. The invention is not dependent on elucidating a new structure, or learning more about the specific strucutures of the promoter, beyond what is in the art. Indeed, it is not clear all of the information the Examiner demands for each of the promoters is known today when transgenic mammary production is a widespread scientific technique and booming commercial enterprise. The level of characterization of the milk specific

promoters found in the art is more than sufficent to show that, in context of this invention, the milk specifc promoters were known.

The milk specific promoters of the art were known to be capable, in their native setting of providing milk specific expression. In addition, they are stucturaly identified and cloned in the milk specific promoter references discussed below. The invention is, however, not disclosed in the references (i.e., the realization that milk specific promoters could be taken out of their native context and be used as taught in the specification to provide mammary specific expression of a heterologous gene in a transgenic animal is not in the art). Even if a detailed correlation of the particular sequence motif within the promoter which confers tissue specificity (as opposed to a more generic or canonical element such as a TATA box) was not in the art, there would still be a sufficient description. This detailed mechanistic understanding of how, on a molecular level, the invention works was not needed for the possession of a milk specific promoter. This is not needed to identify or distinguish the milk specific promoters from other promoters. The milk specificity is revealed by the art-known pattern of expression in the native setting. In essence, the inventors found the art in possession of the milk specific promoters. They discovered a new use for those promoters. The world knew they were there. The inventors showed they could be used to provide mammary specific expression of a heterologous gene in a transgenic animal. The art knew that they were there, in front of milk specific protein encoding sequences, not in front other genes such as actin genes, or hemoglobin or liver or skin specific genes.

We turn now the Examiner's improper analysis and application of the relevant case law and the Guidelines. The Guidelines state that more evidence is required in emerging or unpredictable technologies. Biology is a technology in which some endeavors are predictable and some are unpredictable. Situations in which only function is recited may not satisfy the written description requirement. In particular, where new genes are claimed, a mere recitation of name or function is insufficient. Neither is the case in the instant matter. Structural information, including sequence information, on the milk promoter regions, was known in the art. The claims in the instant matter, unlike those in Amgen, Fiers, and U.C. v. Lilly, are not drawn to novel gene defined only by function in the specification and not known in the art. The facts are much more similar to those in Amgen v. Hoechst and TKT, 314 F.3d 1313 (Fed. Cir. 2003) where the Federal Circuit distinguished sharply between U.C. v Lilly, and Enzo Biochem 296 F.3d 1316 (Fed. Cir. 2002) which dealt with new or unknown biological materials and fact situations which do not involve new or unknown materials. The essential characteristics of the invention in Amgen, Fiers, and U.C. v. Lilly was the determination of a nucleotide sequence not in the art. These fact scenarios dictated holdings in those cases. The present claims are drawn to a new combination of art known elements. Amgen, Fiers, and U.C. v. Lilly, all make it clear that an element which is a new or novel material will require a different (higher) level of detail and disclosure for a sufficient written description than will an element which is known in the art. This has been made abundantly clear when the Federal Circuit has applied the principles of the original cases. See, e.g., Amgen v. Hoechst and TKT:

> We held in Eli Lilly that the adequate description of claimed DNA requires a precise definition of the DNA sequence itself -- not merely a recitation of its function or a

> reference to a potential method for isolating it. 119 F.3d at 1566-67, 43 USPQ2d at 1406 (holding the disclosure of the cDNA sequence of the insulin gene of a rat did not adequately describe the cDNA sequence of the insulin gene of every vertebrate). More recently, in Enzo Biochem, we clarified that Eli Lilly did not hold that all functional descriptions of genetic material necessarily fail as a matter of law to meet the written description requirement; rather, the requirement may be satisfied if in the knowledge of the art the disclosed function is sufficiently correlated to a particular, known structure. See Enzo Biochem, 296 F.3d at 1324, 63 USPQ2d at 1613. Both Eli Lilly and Enzo Biochem are inapposite to this case because the claim terms at issue here are not new or unknown biological materials that ordinarily skilled artisans would easily miscomprehend. Instead, the claims of Amgen's patents refer to types of cells that can be used to produce recombinant human EPO. Thus, TKT can only challenge the adequacy of disclosure of the vertebrate or mammalian host cell -- not the human DNA itself. This difference alone sufficiently distinguishes Eli Lilly, because when used, as here, merely to identify types of cells (instead of undescribed, previously unknown DNA sequences), the words "vertebrate" and "mammalian" readily "convey[] distinguishing information concerning [their] identity" such that one of ordinary skill in the art could "visualize or recognize the identity of the members of the genus." Eli Lilly, 119 F.3d at 1567, 1568, 43 USPQ2d at 1406. Indeed, the district court's reasoned conclusion that the specification's description of producing the claimed EPO in two species of vertebrate or mammalian cells adequately supports claims covering EPO made using the genus vertebrate or mammalian cells, renders Eli Lilly listless in this case. Amgen, 126 F. Supp. 2d at 149, 57 USPQ2d at 1507. (footnotes omitted, emphasis added). Amgen v. Hoechst and TKT, 314 F. 3d at 1332.

The Examiner has ignored this and has treated the instant invention as if the art provided little or no knowledge. The Examiner has grossly and inappropriately misapplied the analytical framework set out in the case law.

Amgen and its progeny stand for the proposition that, absent structural information, the claiming of a gene, by mere function, does not satisfy the written description requirement. The structure of a gene is not implicit in simply stating the name of the gene or stating the desired function, e.g., EPO activity. The instant facts are significantly different. The specification does not merely recite a desired function - which here might be - the production of a heterologous protein (in milk) - but names elements of known structure and function. By naming the elements, it provides, implicitly, sufficient structure to satisfy the written description requirement.

We turn now the issue of whether a representative number of species was known. With regard to the genus of "milk promoters", the specification explicitly describes two types, WAP and α-lactalbumin. Given the level of skill and knowledge in the art, including the fact that the promoters were in the art, and that methods for using and testing promoters were in the art or enabled by the specification, two of seven is sufficient to satisfy the requirement. In the case of

milk promoters, a member of five of the seven general types was known in the art—a remarkably well-characterized genus. In addition to WAP and α-lactalbumin, the specification directs the use of caseins. See page 7, lines 29-30 of the specification. Their relevance is described by the use of that term. Three of the four caseins were well defined in the art. In addition, promoter regions were not all drawn from a single specified but from three different animal species, rat, mouse, and cow. The Guidelines provide that "what constitutes a "representative number" is an inverse function of the skill and knowledge of the art." Given this level of knowledge in the art, one would only need one or a few examples to demonstrate the scope of the claim and possession of an invention that can use any of those species in the milk promoter genus. These examples were present in the Appellant's specification.

In summary, given the level of skill and knowledge in the art, particularly extensive structural knowledge of the promoter regions and the fact that these promoters were known to be capable in their native setting of providing milk specific expression, the disclosure provides an adequate written description of the invention.

II. Written Description

Claims 1-3, 5-9, 11, 16, 17, 19-22 and 24-29 stand rejected under 35 U.S.C. §112, first paragraph, "as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor(s), at the time the invention was filed, had possession of the claimed invention."

This rejection of claims is respectfully traversed.

A. Analysis under the written description Guidelines

The written description rejection is analyzed below in view of the Patent and Trademark Office's written description "Guidelines". The Guidelines provide that: the examiner has the initial burden of overcoming a strong presumption that the written description, as filed, is adequate; that a written description rejection should be rare; and that the analysis for written description is to be made on a case-by-case basis. We turn now to a step-by-step application of the analytical procedure set out in the Guidelines to the instant claims.

1. Analysis of the claims

The Guidelines begin (Guidelines II.A.1) by requiring a careful analysis of the claims. The examiner is instructed to determine if sufficient structures, acts, or functions are recited to make the scope and meaning of the claim clear. The section ends with the provision that:

> The absence of definitions or details for well-established terms or procedures should not be the basis of a rejection under 35 USC sec. 112, paragraph 1, for lack of adequate written description.

As is discussed above, the Examiner has ignored this requirement and has, in essence, written in additional limitations for which she argues there is no written description.

2. Determination of the essential feature of the invention

The Guidelines go on to require that the examiner "Review the entire application to understand what applicant has described as the essential features of the invention" see, the Guidelines, II.A.2. The Guidelines require:

> The examiner is to determine the correspondence between what applicant has described as the essential identifying characteristic features of the invention, i.e., what the applicant has demonstrated possession of, and what applicant has claimed. (II.A.2.)

The invention in the instant application is a DNA construct of a combination of three art-known elements. It is a construct which includes: a region which includes a milk protein promoter, a signal sequence, and a nucleic acid encoding a protein other than the protein normally associated with the milk protein promoter, (sometimes referred to herein as a heterologous gene or protein). Milk promoter regions were known in the art. Structure, including restriction analysis, nucleotide sequence data, and location of specific structures, was known for a broad spectrum of milk promoters.

The essence of the invention, i.e., the essential identifying characteristic feature of the invention, is the combination of these several art-known elements in a new way, namely the functional coupling of milk protein promoter with a signal sequence and a heterologous protein encoding nucleic acid, in a vector. The essential identifying characteristics are, first and foremost, the idea of combining the elements. Clearly that concept of combining is explicitly set out in the claims and throughout the specification. The Appellant is also in possession of the prior art elements which are to be combined. As is discussed below, each of the elements to be combined was known, separately, in the art. By naming and pointing to these well-known elements, the Appellant has demonstrated possession of them for the use in the invention, namely use of them for combination into a vector.

It is important to understand what the invention is and what it is not. The invention is not the discovery of a new genetic sequence, as was, e.g., the invention in Amgen, Fiers, and Lilly. The essential identifying characteristic is not the claiming of a novel gene. Appellant is not attempting to claim a novel gene or even a novel promoter, but rather use of a combination of known elements sufficiently described for the purposes of the claim, by the specification. As is discussed below one major flaw in the Examiner's argument flows from an improper reading of the claims.

The invention is not the elucidation of specific sub-promoter structure, or internal promoter motif, which is responsible in whole or part for mammary specific activity. In other words, the invention is not the finding the smallest fragment of the promoter which has mammary specific expression, or determining what sub-promoter or internal promoter region can be mutated to lose

mammary specific expression, or any other fine structure analysis. The specification, together with the art, points to regions or sequences which contain milk specific promoters (so known because they reside in front of sequences which encode milk specific proteins) gives sufficient structure to identify them from surrounding nucleic acid. It is clear throughout the Examiner's arguments that she has misunderstood the nature of the invention.

3. The Guidelines provide that a written description analysis requires a determination of the level of skill and knowledge in the art

The Guidelines require that a review must be conducted from the standpoint of one skilled in the art at the time the application was filed. (And this of course means the analysis will be different in the case where the claimed material is unknown in the art as opposed to where the claimed material is a combination of known elements.) In conjunction with this requirement that the inquiry be made in light of the art, the Guidelines require that information which is well known in the art does not have to be discussed in detail:

> Such a review is conducted from the standpoint of one of skilled in the art at the time the application was filed, and should include a determination of the field of the invention and the level of **skill and knowledge** in the art. Generally there is an inverse correlation between the level of skill and knowledge in the art and the specificity of disclosure necessary to satisfy the written description requirement. Information which is well known in the art does not have to be described in detail in the specification. (the Guidelines II.A.2, footnotes omitted, emphasis added)

This was reiterated recently in Amgen v. Hoechst and TKT:

> The purpose of the written description requirement is to prevent an applicant from later asserting that he invented that which he did not; the applicant for a patent is therefore required to "recount his invention in such detail that his future claims can be determined to be encompassed within his original creation." Id. at 1561, 19 USPQ2d at 1115 (citation omitted). Satisfaction of this requirement is measured by the understanding of the ordinarily skilled artisan. Lockwood v. Am. Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997) ("The description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). "Compliance with the written description requirement is essentially a fact-based inquiry that will 'necessarily vary depending on the nature of the invention claimed.'" Enzo Biochem v. Gen-Probe, Inc., 296 F.3d 1316, 1324, 63 USPQ2d 1609, 1613 (Fed. Cir. 2002) (emphasis added). Amgen v. Hoechst and TKT, 314 F.3d at 1330.

Bearing in mind that the inquiry must be made from the standpoint of one having the skill and knowledge of the art, that the greater the level of skill and knowledge, the less specificity of disclosure is needed, and that information well known in the art need not be described in detail,

we turn first to the knowledge and skill of the art with regard to the small genus (about 7 types of promoters) of milk promoters and then to the skill in the art, especially with regard to the manipulation of promoters or sequences which include such promoters. Appellant specifically points out that it is not making an enablement-based argument for the satisfaction of the written description requirement (as was made by Fiers in Fiers v. Revel) but is conducting the review of the level of skill and knowledge required for a written description analysis, as mandated by the Guidelines.

As is discussed above, the Examiner has ignored this requirement and has ignored the fact that the art has so well characterized numerous milk specific promoters that one can, with this knowledge provided in the art, show possession of the invention. The Examiner has ignored the teachings of the art, formulated her own way of distinguishing milk specific promoters (the identification of a special motif) and demanded that that formulation be satisfied, even when the art itself provides a different and fully satisfactory way of identifying milk specific promoters and distinguishing them from other promoters.

We now turn to specific examples, drawn from the art, of the "skill and knowledge" in the art. We will first discuss the promoter regions themselves and then discuss general methods for manipulating and using eukaryotic promoters.

i. The level of skill and knowledge in the art with regard to sequences which include a milk promoter

The genus of milk protein promoters was well characterized and defined in the art at the time of filing. This is shown by the five references (all published prior to the filing date of the instant application) discussed below.

These references provide: the cloned genomic sequence, identify the 3' end of the 5' regulatory region, identify characteristic 5' regulatory structures, and provide a significant amount of DNA sequence for the promoter regions, of each of five of the seven types of milk promoters. Appellant notes that information from three different species, rat, mouse, and bovine was in the art at the time of filing. The disclosure of the references is summarized in Table 1.

(1) Table 1. Summary of Milk Promoter Information in Art at the Time of Filing

	Milk Serum Proteins			Caseins			
	α-lact-albumin[1]	β-lactoglobulin	Whey Acid Protein[2] (WAP)	α-casein[3]	β-casein[4]	γ-casein[5]	κ-casein
5' flanking regions cloned in the art?	Yes, 8.5 kb	-	Yes, 9 kb	Yes, 7.1 kb	Yes, 14.6 kb	Yes, 9 kb	-
Restriction Analysis provided in the	Yes	-	Yes	Yes	Yes	Yes	-

art?							
3' end of regulatory region determined in the art?	Yes	-	Yes	Yes	Yes	Yes	-
Promoter region nucleotide sequence data provided in the art?	1,247 bps	-	1,175 bps	680 bps	780 bps	90 bps[5]; 680 bps[3]	-
5' structures, e.g., TATA or CAAT boxes, identified?	Yes	-	Yes	Yes	Yes	Yes	-
RNA transcription start site and sequences preceding that site identified?	Yes	-	Yes	Yes	Yes	Yes	-
Glucocorticoid receptor binding sites, or hormone receptor binding sites	Yes	-	Yes	-	Yes	Yes	-

1. Qasaba and Safaya (1984), *supra.*
2. Campbell *et al.* (1984), *supra.*
3. Yu-Lee *et al.* (1986), *supra.*
4. Jones *et al.*. (1985), *supra.*
5. Yu-Lee and Rosen (1983), *supra.*

(2) Specific examples of individual milk promoters described in the art

(a) α-lactalbumin

Qasaba and Safaya (1984) *Nature* 308:377-380 (submitted herewith as Exhibit A) discloses the nucleic acid sequence of the rat α-lactalbumin gene and identifies promoter region structures. The authors isolated several λ clones which span the rat α-lactalbumin gene. One clone contains at least 8.5 kb of isolated 5' flanking promoter sequence. The reference provides restriction analysis of the region (*Ibid*, Fig. 1, Methods). The reference further provides the nucleotide sequence of 1247 nucleotides of the 5' flanking region (*Ibid*, Fig.1). The 3' end point of this region was defined by primer extension and S1 nuclease mapping of the mRNA. "The 5' end of the rat α-LA mRNA was located at G, position 1,247, by the primer extension method." The authors identify the signature TATA box and promoter elements for progesterone receptor binding. The authors also identify the RNA transcription start site.

(b) Whey Acid Protein (WAP)

Campbell *et al.* (1984) *Nucl. Acids Res* 12:8685-8697 (submitted herewith as Exhibit B) describes the structure of rat and murine WAP promoters. The authors isolated genomic DNA spanning the rat WAP gene. The reference provides a restriction map of the region (*Ibid*, Fig. 1). With regard to the promoter region, the reference provides that at least 9 kb of the isolated DNA is 5' flanking sequence of the WAP gene. The authors defined the 5' flanking region relative the mRNA start site from the cDNA sequence. The sequence of 1175 base pairs of promoter is provided in Fig. 3. The authors identified a TATA box, a CAAT box, glucocorticoid response elements, and a progesterone response element within the promoter. For example, "A competitive DNA cellulose binding assay has identified multiple glucocorticoid receptor binding sites between –566 and –1250 in the rat WAP gene... (*Ibid*, p. 8695)."
The authors also isolated genomic DNA spanning the mouse WAP gene. A restriction map is provided for this DNA. Approximately 2.6 kb of 5' flanking sequence were described. The sequence of 325 base pairs of the promoter was provided. The TATA box and a progesterone receptor binding site were identified.

The rat 5' WAP regulatory sequences are contained in a 12.6 kb partial EcoRI-HhaI fragment. The regulatory sequences closest to the mRNA start site reside on a 2.0 kb EcoRI-HhaI fragment.

(c) α-casein

Yu-Lee *et al.* (1986) *Nucleic Acids Res.*14:1883-1902 (submitted herewith as Exhibit C) describes the structures of the promoter region of rat α-casein and bovine α-casein promoters and compares theses structures with those of rat β-casein and rat γ-casein promoters. The reference provides a restriction map of the 11.5kb rat α-casein locus (*Ibid*, Fig. 2A). With regard

to the promoter region, the reference provides that, "The λα1 clone contains approximately 7.1 kb of 5' flanking DNA..." The 3' end of the 5' regulatory region was determined by comparison to previously published cDNA sequence, primer extension, and S1 nuclease digestion results (see Hobbs and Rosen (1982) *Nucleic Acids Res.*10:8079-8098). The nucleic acid sequence of 680 basepairs of the 5' flanking DNA was disclosed, as well as the transcription start site. The signature TATA box was located.

In addition, the authors isolated λ clones spanning the rat γ-casein gene and the bovine α_{s1}-casein gene. The sequence of 680 base pairs of both these promoters was provided. The authors identify conserved blocks of homology between the rat α-casein promoter, rat β-casein rat promoter, γ-casein promoter, and bovine α_{s1}-casein promoter (e.g., Table 1B).
Stewart *et al.* (1984) *Nucleic Acids Res.*12:3895-3907 (submitted herewith as Exhibit D) report the nucleotide sequence for bovine α-casein, identify the promoter region structures and identifies the transcription start site. The reference provides the sequence of 35 nucleotides of the promoter region and indicates the location of the TATA box.

The rat α-casein 5' regulatory sequences are shown to be contained in a 5.4 kb partial EcoRI-Ndel fragment.

(d) β-casein

Jones *et al.* (1985) *J Biol Chem* 260:7042-7050 (submitted herewith as Exhibit E) report the complete genomic region of the rat β-casein gene including promoter-associated regions. The reference describes 34.4 kb of isolated genomic DNA spanning the rat β-casein locus. The reference provides a restriction map of the entire locus (*Ibid*, Fig. 1 of Supplement, p. 7049). With regard to the promoter region, the reference provides that, "In addition to the 7.2 kb β-casein gene, these clones contain 14.6 kb of 5' flanking DNA. (*Ibid*, p. 7042)." The promoter was further defined relative to the mRNA start site by the cDNA 5' end sequence. The nucleic acid sequence of 780 bp of 5' flanking sequence is provided. The signature promoter elements, TATA box and CAAT box, were within the sequenced region, as were hormone response elements for glucocorticoids and progesterone. The authors also provide the transcription start site for B-casein. As noted above, Yu-Lee *et al.* (1986) also characterized the β-casein promoter and compared it to the bovine α-casein, rat α–casein, and rat γ-casein promoters.

(e) γ-casein

Yu-Lee and Rosen (1983) *J Biol Chem* 258:10794-10804 (submitted herewith as Exhibit F) provide the rat γ-casein gene including promoter region structures. The reference describes 35 kb of isolated genomic DNA spanning the rat γ-casein locus. With regard to the promoter region, the reference provides that, "Approximately 9kb of 5' flanking sequences are found in the λγ9 and λγ10 clones...(p. 10796, col. 1, par 3)." The reference provides a well-characterized restriction map of the region (*Ibid*, Fig. 2). The authors defined this 9 kb region as 5' flanking sequence relative to the 5' end of the mRNA. The 5' end of the mRNA was located by fine

restriction mapping of the genomic sequence relative to cDNA probes. Not only was the promoter region characterized by restriction mapping but also the sequence of 90 basepairs of the promoter was provided. Furthermore, the reference located two typical eukaryotic promoter sequences, a noncanonical TATA box at –29 to –23, and a CAAAT box at –86 to –80. As noted above, Yu-Lee *et al.* (1986) disclosed 680 basepairs of the rat γ-casein promoter, and compared it to the bovine α-casein, rat α–casein, and rat β-casein promoters.

The rat γ-casein 5' regulatory sequences are contained in a 7.7 kb partial EcoRI fragment.

(f) Milk Specific Expression Motifs

Even by the improperly high standards of the rejection, the written description is sufficient. The Examiner demands the identification of some internal milk specific motif. As provided above, this is not needed for a written description of the claimed invention. Appellant points out, however, that the very information demanded by the Examiner is in the art. Thus, even under the Examiner's improperly stringent analytic framework, there is sufficient written description.

Appellant disagrees with the Examiner's assertion that "none of the references provided by the Appellants identify any sequence or structure within the 5' flanking region for genes encoding α-lactalbumin, β-casein, and γ-casein that impart mammary gland specific expression." As is discussed below, the elucidation of special motifs for many of the milk specific promoters the Examiner finds to be insufficiently described in the art is in fact described in the cited milk specific promoter references. What's more, the description is essentially the same as what the art provides for the WAP promoter, which the Examiner admits does have a sufficient written description. Thus, the Examiner's conclusion with respect to WAP requires a finding that the other promoters are adequately described.

Appellant's position is that the information with regard to the correlation of internal motif with function required by the Examiner is not needed to provide a written description. Nevertheless Appellant disagrees with the Examiner's assertion that "none of the references provided by the Appellants identify any sequence or structure within the 5' flanking region for genes encoding α-lactalbumin, β-casein, and γ-casein that impart mammary gland specific expression." As is shown in the following paragraphs hormone binding site motifs were known to be present in diverse milk specific genes.

The milk specific promoter references are replete with descriptions of the special sequences the Examiner insists must be present in order to have a sufficient written description. Yu-Lee (1986), page 1899 (Exhibit C), disclose the presence of glucocorticoid receptor binding sites at various positions within the 5' flanking region of rat α-casein gene, rat γ-casein gene, and bovine α-casein gene. Moreover, Yu-Lee disclose the presence of various other hormone binding sites such as estrogen receptor binding sites and progesterone receptor binding sites in the rat γ-casein gene, the rat and bovine β-casein genes, and the bovine α-casein gene. Yu-Lee further provides that such structures may play a role in tissue-specific expression. See e.g., page 1900. Qasaba et al. (1984) also disclose a putative progesterone receptor-binding site in α-lactalbumin.

Thus, these references do in fact identify the special elements the Examiner asks for. These sequences were not excised and tested in a transgenic animal. That step is part of the invention—that step is supplied by the specification. The art described the promoters, with both canonical or generic promoter structures and with elements believed to cause milk specific expression in the native setting. The inventors supplied a new use for these promoters.

The 5' flanking region of WAP was known to have glucocorticoid receptor binding sites as well as a putative progesterone-binding site. See, e.g., Campbell (1984), page 8695 (Exhibit B filed with the Appeal Brief). The same structures were also known to be present in the 5' flanking region of other milk specific genes. There is no more analysis of the role of these structures in the WAP reference than there are in most of the other milk promoter references. In fact, some of the references may go beyond what is found for WAP. In view of the fact that knowledge of same types structures were known for the WAP promoter and other milk specific promoters, and the Examiner's admission that there is sufficient written description for the WAP promoter, it is difficult to understand how the Examiner can maintain this rejection with regards to other milk-specific promoters.

ii. The level of skill and knowledge in the art with regard to the manipulation and use of eukaryotic promoters

(1) Overview

In accord with the Guidelines and case law, we continue our review of the level of knowledge and skill in the art and specifically to the level of skill in the art with regard to the manipulation of eukaryotic promoters. Appellant provides this information not in an effort to argue enablement but rather to put the meaning of the promoter references in perspective. The references show that the promoter art was, in general, well developed, e.g., in terms of the isolation, recombinant manipulation, and use of mammalian promoters, and notably cell and tissue-specific promoters.

A non-exhaustive list of references which report such work is discussed below. In one example, Ciliberto *et al.* (1985) *Cell* 41:531-540, a promoter containing region was obtained and used to regulate a heterologous gene. The vast majority of nucleotide sequence of the promoter region was not taught by the reference (only 133 of 1200 basepairs of sequence was disclosed in Ciliberto *et al.*). Thus, the entire sequence of the region was not even needed to provide for the construction or use of the promoter.

Most if not all of the significant steps in the isolation of mammalian promoters followed by Ciliberto *et al.* had already been executed for the milk promoters at the time of filing (see the milk promoter references discussed above). Therefore, to use a milk promoter, one would not have to isolate and characterize a promoter from scratch as was done in, e.g., Ciliberto *et al.* One

would not even need to perform all of the steps of the art-known method disclosed in Ciliberto *et al.*

Approximately two years prior to the filing of the application, Campbell *et al.* (1984, *supra*) noted the presence of "105 eukaryotic 5' flanking sequences in GenBank™ (*Ibid*, p. 8694)." By the filing date, it was routine in the art to obtain mammalian promoters and to couple them to heterologous genes, as is discussed in the following examples.

We now turn to specific examples in the art of the skill and knowledge with regard to eukaryotic promoters.

(2) Examples of the level of skill and knowledge in the art with regard to the making and using of eukaryotic promoters

(a) Ciliberto *et al.* (1985) *Cell* 41:531-540

Ciliberto *et al.* (submitted herewith as Exhibit G) obtained genomic nucleic acids, determined the 3' end of the 5' regulatory region, isolated a promoter-containing fragment, and coupled it to a heterologous sequence. In particular, the authors isolated λ clones spanning the human α1-antitrypsin locus, mapped the transcription initiation site by primer extension, and S1 nuclease digestion, and thereby defined the α1-antitrypsin promoter as the region immediately 5' to the mRNA transcription start site. The authors fused a heterologous CAT gene to 1200 base pairs of 5' flanking sequence, and found that the resulting construct not only had promoter activity, but the promoter activity was cell-type specific. Fig. 11 (*Ibid*) illustrates that this promoter fusion construct was active in Hep3B cells but not HeLa cells.

Notably, these results in at least Ciliberto *et al.* were obtained without the vast majority of nucleotide sequence of the promoter region (only 133 of 1200 basepairs of sequence was disclosed). Thus, the sequence of the region was not needed to enable the construction. Note that most if not all of the significant steps in the isolation of mammalian promoters followed by Ciliberto *et al.* had already been executed for milk promoters at the time of filing (see the milk promoter references discussed above). Therefore, to use a milk promoter, one would not have to isolate and characterize a promoter from scratch as was done in, e.g., Ciliberto *et al.*

(b) Walker *et al.* (1983) *Nature* 306:557-561

Walker *et al.* (submitted herewith as Exhibit H) demonstrated that a heterologous gene fused to the promoter containing region of the insulin and chymotrypsin gene is expressed only in specific cells, i.e., those that express the endogenous gene. With regard to the promoters, the reference provides that:

> DNA sequences containing the 5'-flanking regions of the insulin and chymotrypsin genes were linked to the coding sequence of the chloramphenicol

acetyltransferase (CAT) gene. The insulin gene recombinant elicits preferential expression of CAT activity when introduced into cells producing insulin; similarly the chymotrypsin gene recombinant elicits preferential expression in chymotrypsin-producing cells.

(c) Krumlauf *et al.* (1985) *Mol Cell Bio* 5:1639-1648

Krumlauf *et al.* (submitted herewith as Exhibit I) demonstrated *in vivo* promoter activity for isolated 14 kb 5' flanking DNA of the mouse α-fetoprotein. The isolation of this regulatory region was previously described in Ingram *et al.* (1981) *Proc Natl Acad Sci USA* 78:4694-4698. This region and a smaller 7kb region were cloned upstream of a minigene which serves a reporter for promoter activity. The resulting constructs were microinjected mice. The authors "conclude that the modified genes, which included either 7 or 14 kilobase pairs of 5' flanking DNA, contained the DNA sequence information to direct both tissue-specific expression and developmental regulation."

(d) Ott *et al.* (1984) *EMBO J* 3:2505-2510

Ott *et al.* (submitted herewith as Exhibit J) demonstrated that a heterologous gene fused to the promoter containing region of the rat albumin gene is expressed only in specific cells, i.e., those that express the endogenous gene. From a plasmid subclone of this region, the authors "constructed a transient expression vector containing 400 bp of rat albumin gene immediate 5'-flanking sequences inserted 5' to the bacterial enzyme chloramphenicol acetyl transferase (CAT). ... The albumin flanking sequences are able to direct highly efficient CAT expression, compared with the control vectors, only in cells which express their own albumin gene..." (The isolation of the rat albumin regulatory region was previously described in Sargent *et al.* (1981) *J. Mol. Cell. Biol.*1:871-883.)

(e) Ornitz *et al.* (1985) *Nature* 313:600-602

Ornitz *et al.* (submitted herewith as Exhibit K) "demonstrate that a fusion gene containing only 213 base pairs of [rat] elastase I gene sequence directs expression of hGH [a reporter] in pancreatic acinar cells." Transgenic mice were generated with the fusion gene and the hGH reporter was not expressed in any of the tissues tested, except the pancreas, the tissue wherein the endogenous elastase I gene is expressed. The isolation of the rat elastase I promoter DNA was previously reported in Swift *et al.* (1984) *Cell* 1984 38:639-646 and Sargent *et al.* (1979) *Proc Natl Acad Sci USA* 76:3256-3260.

(f) Palmiter *et al.* (1982) *Nature* 300:611-615

Palmiter *et al.* (submitted herewith as Exhibit L) coupled a region which included the mouse metallothionein-I gene promoter to nucleic acid encoding the rat growth hormone. Mice microinjected with this DNA construct expressed the rat growth hormone gene in liver indicating that the promoter was functional *in vivo*. In addition, Palmiter and Brinster in US 4,579,821

describe a plasmid which "include[s] a DNA sequence coding for herpes simplex virus thymidine kinase which is operatively associated with the promoter/regulator DNA sequence of the mouse metallothionein-I gene." The isolation of the promoter of the mouse metallothionein-I gene promoter by methods similar to those described below was described in Durnam *et al.* (1980) *Proc Natl Acad Sci USA* 77:6511-6515.

(g) Magram *et al.* (1985) *Nature* 313:338-340

Magram *et al.* (submitted herewith as Exhibit M) demonstrated that the "5' portion of the mouse β^{dmaj} adult globin gene and 1.2 kilobases (kb) of 5' flanking DNA, joined to the 3' portion of the human β-globin gene..." was sufficient to function as a cell specific promoter. The authors "conclude that the mouse/human hybrid β-globin gene in three different transgenic mouse lines is inactive in embryonic blood cells, and is first expressed in the fetal liver erythroblasts. This pattern of switching is identical to that of the endogenous adult β-globin genes...". The isolation of genomic DNA spanning the mouse β-globin gene had been previously reported.

(h) Ishii *et al.* (1985) *Proc Natl Acad Sci USA* 82:4920-4924

Ishii *et al.* (submitted herewith as Exhibit N) isolated more than 10 kb of genomic DNA in λ clones spanning the human EGF-receptor locus using degenerate oligonucleotides. Further they have "localized the EGF receptor gene 'promoter' in cloned human genomic DNA (*Ibid*, p. 4923)." The promoter was defined relative to the mRNA start site as determined by primer extension and S1 nuclease mapping. The nucleotide sequence of 460 base pairs of the promoter was provided. The authors demonstrated that the promoter was functional in an *in vitro* transcription assay.

(i) Melton *et al.* (1984) *Proc Natl Acad Sci USA* 81:2147-2151

Melton *et al.* (submitted herewith as Exhibit O) isolated 60 kb of genomic DNA spanning the mouse HPRT gene, of this, greater than 10 kb was 5' flanking sequence. The authors demonstrated that the first 850 basepairs of 5' flanking sequence is a functional promoter in a construct containing a cDNA fusion.

(j) Reynolds *et al.* (1984) *Cell* 38:275-285

Reynolds *et al.* (submitted herewith as Exhibit P) used a clone walking technique to isolate more than 30 kb of DNA spanning the hamster HMG CoA reductase locus, of which approximately 1 kb was 5' flanking sequence. The promoter was defined by the 5' end of the mRNA, determined by primer extension and S1 nuclease protection. About 300 nucleotides of the promoter were sequenced. The promoter was fused to the CAT gene and showed activity in transfected cells.

(k) Valerio *et al.* (1985) *EMBO J* 4:437-443

Valerio *et al.* (submitted herewith as Exhibit Q) isolated 66 kb as cosmid clones spanning the human adenosine deaminase gene, approximately 10 kb of this region is 5' flanking sequence. The 3' boundary of the promoter was defined by S1 nuclease and primer extension experiments. The authors demonstrated that 135 base pairs of the 5' flanking sequence when fused to a cDNA was an active promoter in cultured cells. The sequence of the region was provided.

4. The Guidelines require the determination of whether the appellant was in possession of the claimed invention

The next step in the Guidelines requires a determination of:

> Whether there is Sufficient Written Description To Inform a Skilled Artisan That Applicant Was in Possession of the Claimed Invention as a Whole at the Time the Application Was Filed (the Guidelines, II.A.3.)

The Guidelines make no a priori rules as to how possession can be shown. In fact, the Guidelines provide the very opposite by explicitly stating that "possession may be shown in a number of ways." (II.A.2.a.). The Guidelines provide that possession can be shown by (a) actual reduction to practice, (b) reduction to drawings, or (c):

> ...by disclosure of sufficiently detailed relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, [39] i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.[40] What is conventional or well known to one skilled in the art need not be disclosed in detail.[41] If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met.[42] (emphasis added).

Appellant points out the lack of rigid a priori rules about what constitutes satisfaction of the requirement and an emphasis on factual analysis. The Guidelines talk about identifying characteristics. The art provided extensive identifying characteristics, including sequence determination, identification of canonical and specific promoter motifs, and the structural association of the promoter regions with milk specific proteins. Thus, the art taught milk specific genes and the promoter structures which flank the coding regions. The Examiner has never addressed that issue and has never said why that is not a sufficient identifying characteristic. The approach required by the Guidelines is the opposite of an automatic application of prior fact specific holdings to very different inventions. The Guidelines, quite properly, do not go beyond the case law. It is clear from a close reading of the Guidelines that

the drafters were very careful to reflect the distinctions found in the cases, which make a requirement for the recitation of the complete sequence only under specific circumstances. The case law is discussed below but we provide here a short section from Lilly.

In particular, the Court in Lilly was careful to limit the holding to particular circumstances, circumstances which differentiate the instant matter. Like its predecessors, the need for sequence data in Lilly was in the context of a claim, the essence of which was, the elucidation of a novel nucleic acid sequence. When speaking more broadly, the court was careful to qualify its remarks.

> Accordingly, naming a type of material known to exist, in the absence of knowledge as to what the material consist of, is not a description of that material. (emphasis added).

That is a critical distinction, we are not facing the situation which presents an absence of knowledge as to the claim element--it is known in the art. Thus here, the naming of the claimed element accomplishes a great deal more and satisfies the written description requirement.

(a) In view of the state of the art, naming the art-known promoters is sufficient to describe them

As discussed above, the genus of milk protein promoters was well characterized and defined in the art at the time of filing. This is shown by the five references (all published prior to the filing date of the instant application) discussed above.

These references provide the cloned genomic sequence, identify the 3' end of the 5' regulatory region, identify characteristic 5' regulatory structures, and provide a significant amount of DNA sequence for the promoter regions, of each of five of the seven types of milk promoters. The disclosure of the references is summarized in Table 1. In addition, as is discussed in section II.3.ii(2), page 15 above, and there was generally a highly developed understanding of eukaryotic promoters.

The identifying characteristic provided by the Appellant for a sequence or region which includes a milk specific promoter is the name of the promoter. Given the fact that these promoter regions were known in the art, that is sufficient--it is sufficient in that it clearly conveys what was invented--the "essential goal" of the written description requirement. To point to the promoter by naming it, when, as here, the art is replete with structural and functional characterization of the promoter, says "use this specific structurally characterized art-known element." The degree of detail needed to convey the realization that the inventor was in possession depends on the essential character of the invention and the level of skill and knowledge in the art. If the art were devoid of information as to milk specific genes and promoters, a great level of detail would of course be called for. However, in this case, the level of knowledge and skill in the art is considerable and naming the known element is sufficient.

The knowledge of milk protein promoters, including partial sequence information, and namely their position within the structure of genes which encode milk specific proteins was well developed in the art. In the light of this knowledge, the essential nature of the invention, and the level of skill in the art, recitation of the promoter demonstrates possession. Once the inventor teaches one to combine the elements, very little, indeed no more than identifying the element, is needed to demonstrate possession.

The Guidelines explicitly recognize the level of description needed depends on how much was known in the art about the subject matter. The Guidelines recognize and:

> ...distinguish between novel and old elements in a claim to clarify that the amount of written support needed in an application can vary depending on the general knowledge that was readily available in a particular art. (See PTO's response to comments in the Guidelines).

Section II.A.3.a (1) (c) (ii) of the Guidelines discusses what will satisfy the written description requirement "if the application does not disclose the complete structure of the claimed invention." The examiner is instructed to:

> ...determine whether the specification discloses other relevant identifying characteristics sufficient to describe the claimed invention in such full clear, concise, and exact terms that a skilled artisan was in possession of the claimed invention. (footnotes omitted)

The Guidelines explicitly require that printed publications should be relied on to determine the level of knowledge and skill in the art. With regard to this point, the Examiner is directed to the section above which shows that printed publications described the promoters including sequence data.

(b) Application of the analytical framework set out in Amgen, Fiers and U.C. v. Lilly and their progeny does not require correlation of a particular milk specific motif with activity

The Guidelines state that more evidence is required in emerging or unpredictable technologies. Biology is often referred to as an unpredictable art. That is of course a generalization. Biology is a technology in which some endeavors are predictable and some are unpredictable. Situations in which only function is recited may not satisfy the written description requirement. In particular, where new genes are claimed a mere recitation of name, or function, is insufficient. But, the instant case is not one where the structure is unknown to the inventor and the art. Structural information, including sequence information, on the milk promoters was known in the art. The claims in the instant matter, unlike those in Amgen, Fiers, and U.C. v. Lilly, are not drawn to novel gene sequence defined only by function in the specification, and having no

sequence structure in the art. The essential characteristics of the invention in Amgen, Fiers, and U.C. v. Lilly were the determination of a nucleotide sequence not previously in the art.

(i) Amgen

In Amgen, the Court considered what was needed for conception for a claim directed to a newly discovered gene sequence. The claims at issue in Amgen were directed to a purified and isolated DNA sequence. The court focused on knowledge of the nucleotide sequence in terms of determining whether conception had occurred. For at least some claims considered in Amgen, see, e.g., claim 2 of the Amgen patent, the gene was described and claimed solely in terms of its function. Thus, this was the only limitation in a setting where the essential character of the invention was the determination of a nucleotide sequence of a previously uncharacterized gene. There was nothing else one could look to know if the inventor was in possession of the invention and to be able to distinguish the invention from other materials. Once one realizes that it is the discovery of the specific sequence which is the invention in Amgen, it is really not surprising that the court found that there was no invention. In contrast, in the instant invention, structural knowledge of the elements of the claim was in the art. Unlike the situation in Amgen, in the instant case, the art was in the possession of all of the separate elements of the claim. In Amgen, the court stated explicitly that "The structure of this DNA sequence was unknown until 1983, when the gene was cloned by Lin...." 927 F. 2d at 1206.

In the invention in Amgen, a new gene sequence, and the instant invention, a vector having art known elements, both the new gene sequence and the vector, in a physical sense, are made of nucleic acid, but otherwise they are quite different. Detailed base-by-base sequence was clearly needed in the case of Amgen, where that (i.e., the newly discovered sequence) was the invention, it was what was new over the art, and, most important, it was needed to distinguish other materials. In the Amgen invention, knowledge of base-by-base sequence was the invention. In the instant case, it is irrelevant.

Nothing in the Amgen holding says that a sequence (let alone a complete sequence or the correction of some specific motif within the sequence with a specific function) is required to meet the written description in every invention which relates to a nucleic acid. Indeed, the holding was explicitly limited to the invention of genes:

> We hold that when an inventor is unable to envision the detailed constitution of a gene so as to distinguish it from other materials, as well as a method for obtaining it, conception has not been achieved until reduction to practice has occurred, *i.e.*, until after the gene has been isolated. Amgen at 1206 (emphasis added).

Even this language is conditional, note the use of the term "when" in the first sentence of the quoted passage.

The court relied on structure, in that instance, the knowledge of sequence to distinguish the claimed gene from other genes:

> Thus, until Fritsch had a complete mental conception of a purified and isolated DNA sequence encoding EPO and a method for its preparation, in which the precise identity of the sequence is envisioned, or in terms of other characteristics sufficient to distinguish it from other genes, all he had was an objective to make an invention which he could not then adequately describe or define. Amgen at 1206.

The art provides the region which contains the milk specific promoter. The correlation of the specific individual motifs which might be within that region argued for by the Examiner, is simply not needed to distinguish the claimed invention from other materials. As discussed at numerous points elsewhere herein, that can be accomplished in other ways which were known in the art.

Appellant is not arguing that the Amgen Court limited its decision to the exact facts of the case. The decision did, however, appear to clearly limit it to a claim to a gene. Even if this is not the case, it is beyond argument that the court in Amgen did not require a complete DNA sequence in every claim which recites a composition which includes a nucleic acid.

The instant fact pattern differs from those in Amgen in at least two ways: first the claimed invention is not a novel gene, and second there is a very good way to distinguish milk specific promoters from other promoters, namely they are part of the structure of genes which encode proteins which are found specifically in milk. There was no such guidance in the facts of Amgen.

Amgen and its progeny stand for the proposition that, absent structural information, the claiming of a gene, by mere function, does not satisfy the written description requirement. (As discussed below this proposition is explicitly relevant in Lilly). The structure of a gene is not implicit in simply stating the name of the gene or stating the desired function, e.g., EPO activity. The instant facts are significantly different. The specification does not merely recite a desired function - which here is - the production of a heterologous protein (in milk) - but names elements of known structure and function, by naming the elements, it refers to structures in the art and provides sufficient structure information to satisfy the requirement.

(ii) Fiers

In Fiers v. Revel, 984 F. 2d 1164 (Fed. Cir. 1993), the applicants attempted to establish conception of a novel (i.e., unknown in the art) gene by providing a protocol for isolating the gene but no sequence data.

The Fiers court held:

> A bare reference to a DNA with a statement that it can be obtained by reverse transcription is not a description; it does not indicate that Revel was in possession of the DNA. Revel's argument that correspondence between the language of the count and language in the specification is sufficient to satisfy the written description requirement is unpersuasive when none of that language particularly describes the DNA.
>
> As we stated in Amgen and reaffirmed above, such a disclosure just represents a wish, or arguably a plan, for obtaining the DNA. If a conception of a DNA requires a precise definition, such as by structure, formula, chemical name, or physical properties, as we have held, then a description also requires that degree of specificity. To paraphrase the Board, one cannot describe what one has not conceived. Fiers at 1171

The court further held:

> We thus determined that, irrespective of the complexity or simplicity of the method of isolation employed, conception of a DNA, like conception of any chemical substance, requires a definition of that substance other than by its functional utility. Fiers at 1169.

The recitation of the name of the promoter, where the promoter is known and well characterized (and in fact largely sequenced) in the art, is far more than the mere recitation on the name of an unsequenced gene. The instant fact pattern differs in at least two ways: first the claimed invention is not merely a wish or set of instructions for discovering something, and second, there is a very good way to distinguish milk specific promoters from other promoters, namely they are part of the structure of genes which encode proteins which are found specifically in milk. There was no such guidance in the facts of Fiers.

(iii) U.C. v. Lilly

In U.C. v. Lilly, the Court applied the teachings of Amgen to a claim drawn to novel cDNAs encoding insulin. In this case, the specification failed to disclose the sequence of the gene, and as would be expected in claiming a novel gene, the claimed subject matter was not taught in the

art. The Court found the written description requirement was not met and said, "The name cDNA is not itself a written description of that DNA; it conveys no distinguishing information concerning its identity." That is the correct result because the art did not provide the needed sequence thus simply naming it meant little. In contrast, the instant situation, the name of the promoter element conveys "distinguishing information concerning its identity", because of the level of knowledge provided by the art in the instant case.

Like its predecessors, the need for sequence data in Lilly was in the context of a claim, the essence of which was, the elucidation of a novel nucleic acid sequence. When speaking more broadly, e.g., where knowledge of the structure is in the art, the court was careful to qualify its remarks.

> Accordingly, naming a type of material known to exist, in the absence of knowledge as to what the material consist of, is not a description of that material. (emphasis added).

That is a critical distinction, we are not facing the situation which presents an absence of knowledge as to the claim element--it is known in the art. Thus here, the naming of the claimed element accomplishes a great deal more and satisfies the written description requirement.

(iv) Amgen v Hoechst and TKT

In Amgen v Hoechst and TKT, 314 F. 3d 1313 (Fed. Cir. 2003), the Federal Circuit applied the principles of UC v. Lilly, and Enzo Biochem to facts that are far more like the instant case than were the facts in UC v. Lilly or Amgen. In Amgen v Hoechst and TKT, TKT argued that Amgen's patent failed to provide sufficient written description for certain cells. TKT argued that there was not a written description for the term vertebrate and mammalian host cells, entities that were known in the art. TKT urged an application of Amgen and UC v. Lilly similar to that adopted by the Examiner in this matter. The Federal Circuit roundly rejected TKT's analysis:

> More recently, in Enzo Biochem, we clarified that Eli Lilly did not hold that all functional descriptions of genetic material necessarily fail as a matter of law to meet the written description requirement; rather, the requirement may be satisfied if in the knowledge of the art the disclosed function is sufficiently correlated to a particular, known structure. See Enzo Biochem, 296 F.3d at 1324, 63 USPQ2d at 1613. Both Eli Lilly and Enzo Biochem are inapposite to this case because the claim terms at issue here are not new or unknown biological materials that ordinarily skilled artisans would easily miscomprehend. Instead, the claims of Amgen's patents refer to types of cells that can be used to produce recombinant human EPO. Thus, TKT can only challenge the adequacy of disclosure of the vertebrate or mammalian host cell -- not the human DNA itself. This difference alone sufficiently distinguishes Eli Lilly, because when used, as here, merely to identify types of cells (instead of undescribed, previously unknown DNA sequences), the words "vertebrate" and "mammalian" readily "convey[] distinguishing information

> concerning [their] identity" such that one of ordinary skill in the art could "visualize or recognize the identity of the members of the genus." Eli Lilly, 119 F.3d at 1567, 1568, 43 USPQ2d at 1406. Indeed, the district court's reasoned conclusion that the specification's description of producing the claimed EPO in two species of vertebrate or mammalian cells adequately supports claims covering EPO made using the genus vertebrate or mammalian cells, renders Eli Lilly listless in this case. Amgen, 126 F. Supp. 2d at 149, 57 USPQ2d at 1507. (footnotes omitted, emphasis added). Amgen v. Hoechst and TKT, 314 F.3d at 1332.

(v) Summary of the Case Law

In summary, the milk promoter regions were known in the art. The art taught the structure, including sequence data for milk promoter containing regions and elucidation of particular motifs for milk specific promoters. See the data summarized in Table 1. This situation is entirely different from the facts in Amgen, Fiers, and U.C. v. Lilly, where the Applicants claimed novel genes, with nothing other than function.

5. The Specification satisfies the written description requirement for the species claims, i.e., claims 17 and 22.

We turn now to the question of written description for the claimed species.

The Guidelines require that for each claim drawn to a single species the examiner should determine (a) whether an actual reduction to practice is described, (b) if the invention is complete as evidenced by a reduction to drawings, or (c):

> Whether the invention has been set forth in terms of distinguishing identifying characteristics as evidenced by other descriptions of the invention that are sufficiently detailed to show that applicant was in possession of the invention. (Guidelines II.A.3.1)

Each species claimed is now analyzed. Although other species are disclosed in the specification, the only species claims are to α-lactalbumin, see claims 17 and 22. The detailed description is met by satisfying criteria (c) set out in the Guidelines.

a. Claims 17 and 22

α-lactalbumin promoter-containing regions were known in the art. See Qasaba and Safaya and the discussion thereof in section II.3 (2)(a), page 15 above. The written description for α-lactalbumin is provided for by naming the promoter.

6. The specification provides a written description of the claimed Genus of claims 1, 2, 5, 6, 7, 8, 9, 11, 19, 20, 24, 25 and 29.

We turn now to written description for the genus of "milk protein promoters".

a. The Genus

We first consider the genus of milk promoters. It is important to keep in mind that the genus of milk specific promoters is very small. Limited might be a better choice of works, but by small, it is meant not only numerically but also, and perhaps more properly, limited in the sense that, in nature, these promoters are found only within the structure of a gene which encodes a milk specific protein. This doesn't mean that Appellant does not need to describe the genus, but as discussed below, Appellant does describe them and a large portion, five of seven, of these types of promoters were known in the art. It is noted that all the promoters share common canonical structures and linkage to milk specific protein encoding sequences. The genus consists of about seven types of promoters. They are as follows:

Whey acid promoter (WAP);
α - lactalbumin;
B - lactoglobulin;
α - casein;
B - casein;
K-casein; and
γ-casein.

The genus can be divided into to "sub" genera: the "milk serum proteins" which consists of three proteins (WAP, α-lactalbumin, and B-lactoglobulin); and the "caseins", which consists of four proteins (α, B, K, and gamma casein), see claims 16, 17, 21, 22, 26, 27 and 28. As is shown in Table 1, regions which include five of the seven types of milk promoters were known in the art, including partial sequence, at the time of filing. (For the subgenera, promoter-containing regions for 2 of 3 were known for the milk serum proteins; and promoter-containing regions for 3 of 4 were known for the caseins.) Thus, these genera were exceedingly well characterized.

As is discussed above, the Guidelines provide for several ways in which the written description requirement can be satisfied, by: (a) actual reduction to practice; (b) reduction to drawings; or (c) by a disclosure of relevant identifying characteristics sufficient to show possession of the genus.

We now turn to a description of the promoter species provided in the specification.

b. The species described in the specification.

(i) The WAP promoter

Constructs containing the WAP promoter were made and deposited with the ATCC as ATCC No. 67032 and 67033. See page 10 and 12 of the specification.

Figures 1-5 present drawings of a WAP promoter-containing vector of the invention. The specification identifies the WAP promoter (see, e.g., page 9 of the specification) by that term, which in view of the level of knowledge and skill in the art, see, e.g., Campbell et al. (1984) discussed above, is a description sufficient to show possession.

Thus, for the WAP promoter, the specification satisfies the written description requirement in all three ways set out in the Guidelines.

(ii) The α-lactalbumin promoter

The specification identifies the α-lactalbumin promoter (see page 4), by its art recognized name, which in view of the level of knowledge and skill in the art is a description sufficient to show possession. As is discussed herein, Qasaba and Safaya et al. (1984) discussed above, provides a detailed characterization of the α-lactalbumin promoter.

(iii) The casein promoters

The specification teaches that the casein promoters (see pages 2 and 15) should be used. In view of the level of knowledge and skill in the art, this description is sufficient to show possession. As is discussed herein, Yu-Lee et al. (1986), Jones et al. (1985) and Yu-Lee and Rosen (1983) provide detailed characterization of the 3 of the 4 casein promoters.

7. A Representative Number of the Members of the Milk Promoter Genus are described.

The Guidelines provide that the written description requirement for a claimed genus may be satisfied by sufficient description of a representative number of species, by the same standards as discussed for species claims, see, the Guidelines II.3.a.(2). The Guidelines provide as follows:

> A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. What constitutes a "representative number" is an inverse function of the skill and knowledge in the art. Satisfactory disclosure of a "representative

> number" depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. In an unpredictable art, adequate written description of a genus which embraces widely variant species *cannot* be achieved by disclosing only one species within the genus.[50] Description of a representative number of species does not require the description to be of such specificity that it would provide individual support for each species that the genus embraces.[51]

With regard to the genus of "milk promoters", the specification explicitly describes two specific types, WAP and α-lactalbumin, and one sub-genus, namely the caseins. See Section 6.a above for a discussion of the relationship of genus, sub-genus and species of milk proteins. Given the level of skill and knowledge in the art, including the fact that the promoters were in the art, and that methods for using and testing promoters were in the art or enabled by the specification, two of seven is sufficient to satisfy the requirement. The specification goes even further and designates a sub-genus of milk proteins, the caseins. The Guidelines provide that "what constitutes a "representative number" is an inverse function of the skill and knowledge of the art." Here five of the seven were well characterized in the art. Surely, that is a high level of skill and knowledge. Given this level of knowledge in the art, one would only need one or a few examples to demonstrate possession of an invention that can use any of those species in the milk promoter genus.

Although individual casein promoters are not expressly named, the specification directs the use of "caseins". Their relevance is described by the use of that term. Three of the four caseins were well defined in the art. The Appellant did not explicitly name the casein promoters but specified the broad term casein. Although there was no individual naming, this together with the specific naming of the others helps show one of ordinary skill what is meant by milk promoters and thus put one in possession of the genus. U.C. v. Lilly supports the view that there is not just one way to describe a genus.

In Lilly, the Court considered whether the description of a single cDNA species provided a description of two very large genera, namely vertebrate and mammalian. The court held that:

> A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus. (emphasis added)

However, the court did not close the door to other methods of meeting the requirement:

> However, it may not be necessary to enumerate a plurality [*28] of species if a genus is sufficiently identified in an application by "other appropriate language." (citations omitted). We will not speculate in what other ways a broad genus of genetic material may be properly described, but it is clear to us, as it was to the district court, that the claimed genera of vertebrate and mammal cDNA are not described by the general language of the '525 patent's written description supported only by the specific nucleotide sequence of rat insulin.

We note also that for some milk promoters, namely the WAP and α-casein, promoters of more than one species were known. In the case of WAP, rat and murine were known. In the case of α casein, rat and bovine were known. We note that all species of a genus need not be described, see the Guidelines, which provide:

> Description of a representative number of species does not require the description to be of such specificity that it would provide individual support for each species that genus embraces.[51]

The content of footnote 51 is relevant to this inquiry, as even in the case of a new gene, the number of species required is limited. Footnote 51 provides:

> For example, in the genetic arts, it is unnecessary for an applicant to provide enough different species that the disclosure will permit one of skill to determine the nucleic acid sequence of another species from the application alone. The stochastic nature of gene evolution would make such a predictability nearly impossible. Thus, the Federal Circuit could not have intended that the representative number requires predictability of sequences.

8. <u>A representative number of species of the Milk Serum Genus are described.</u>

Claims 16, 21, 26, 27 and 28 are directed to the sub-genus of milk serum promoters. This sub-genus includes three types of promoters-namely, WAP, α-lactalbumin and β-lactoglobulin. As is discussed above, the WAP and α-lactalbumin species are described. Thus, 2 of the 3 types of milk serum promoters are described.

The Examiner has failed to meet the burden of presenting by a preponderance of evidence why a person skilled in the art would not recognize in the disclosure a description of the invention defined by the claims.

9. There is sufficient description of the sub-genus of casein promoters

Although individual casein promoters are not expressly named, the specification directs the use of "caseins". Their relevance is described by the use of that term. Three of the four caseins were well defined in the art. The Appellant did not explicitly name the casein promoters but specified the broad term casein. Although there was no individual naming of the species of caseins, a large portion of the casein species which make up this sub-genus were well known and the naming of casein generally was enough to describe this sub-genus. Thus, the naming of the sub-genus itself put one in possession of the casein promoters.

B. Responses to specific remarks made in the Office Action under the Written Description Rejection

We turn now to specific remarks made in the last Office Action. The remarks are addressed in the order they appear in the Office Action.

On page 7, last paragraph, of the Office Action, the Examiner admits that "Qasba et al (Exhibit A), Yu-Lee et al. (Exhibit C), Jones et al (Exhibit E) and Yu-Lee and Rosen (Exhibit F) teach the genomic sequence and structure for, respectively, α-lactalbumin, α-casein, β-casein and γ-casein." The Examiner then goes on to state that

> While each references teaches the presence of putative TATA boxes and CAAT boxes, the references never disclose the complete 5' structure that comprises the various milk promoter regions. There is obviously more to identifying a promoter than the presence of regions that resemble TATA box or CAAT boxes, as all promoters, even prokaryotic promoters, have these sequences. However, the claims require milk protein promoters. These are promoters that function in the mammary gland, and have some special structural or sequence that affords them this designation. Thus, more structure is needed that TATA boxes and CAAT boxes to promoter the mammary gland location of expression as dictated by the claims, and indicated as necessary in the specification to make transgenic non-human mammals expression of a heterologous protein in their milk. None of the references provided by applicant teach the location of any sequence or structure within the 5' flanking region for genes encoding α-lactalbumin, α-casein, β-casein and γ-casein that impart mammary gland specific expression.

This statement shows one of the fatal weaknesses of the written description rejection, namely the Examiner's insistence on specific identification of elements (within the promoter region) which are specifically responsible for mammary specific expresssion. These elements are not claimed—the Examiner is not foucusing on the claimed invention. Knowledge of these elements is not required to practice or describe the invention. The art provides other ways of identifying milk specific promoters and distinguishing them from other promoters.

The Examiner's insistence on a description of such elements might carry more weight if there were no other way of distinguishing a milk specific promoter from other promoters, e.g., a liver specific promoter. But the art does provide another way. The art provides, as part of its characterization of the milk specific genes, proteins and promoters, a way of identifing milk specific promoters or telling one what they would look like. Quite simply, a milk specific promoter can be identified from nature by the simple and elegant fact that it is part of the structure of a gene, which encodes a milk specific protein. Milk specific proteins, caseins, lactalbumin, WAP, etc., and their genes, are a distinct and well characterized group of proteins (and genes). One can look to these promoters, known in the art to have, in nature, in their native setting, milk specific expression. The Examiner argues that "None of the references provided by applicant teach the location of any sequence or structure within the 5' flanking region for genes encoding α-lactalbumin, α-casein, β-casein and γ-casein that impart mammary gland specific expression." That is incorrect on several levels. Perhaps most importantly, the location of milk specfic promoter regions is taught, the Examiner's proposed element is not identified because there is no need to identify it. The Examiner confuses her superfluous requirement with the claimed invention.

In addition, as is discussed elsewhere herein, the Examiner is incorrect even with regard to the elements she proposes. The references do provide guidance on the presence of hormone binding site motifs. But even if such teaching had been absent, the Examiner's argument is still fatally flawed.

The Examiner argues that "There is obviously more to identifying a promoter than the presence of regions that resemble TATA box or CAAT boxes, as all promoters, even prokaryotic promoters, have these sequences. However, the claims require milk protein promoters." The Examiner is right, it does require more, but that "more" is supplied by the specification and the art, namely that the desired promoter region is associated with, is part of the structure of, a gene for a protein which is found specifically in the milk. That is sufficient to satisfy the written description requirement. The Examiner improperly ignores this and formulates an alternative way of satisfying the requirement—namely, the correlation milk specific acitivity with specific sub-promoter or internal promoter structures within the region required in the Appellant's claims. That alternative formulation is not necessarily of relevance to the claimed invention.

Appellant urges close examination of the claims, particularly claim 19 which makes the nature of the claims particularly explicit. The claims are not directed to and do not mention these sub-promoter structures or motifs, the claims merely say to take the larger region and use it. The inventors provided a written description for their invention. The Examiner is demanding a discosure that would be more relevant to a different invention, namely, a claim directly to the motifs mentioned above. Thus, the Examiner is really focusing on a different invention, one which might be claimed as "a nucleic acid consisting essentialy of SEQ ID NO. 1 (wherein that sequence is, e.g., an internal fragement of one of the sequences described in the art or included in the claimed constructs). The issue of whether the inventors have provided a written description for that subject matter is irrelevant.

Contrary to the Examiner's assertions, the milk specific promoters are well characterized in the art, and as is discussed in great deal in the section on promoter region references above, there is a lot of description to be dealt with if one is going to attempt to argue that such intimately detailed promoters are not in the posession of the art. Indeed, the remarkable thing about this case is that so much was actually known. The Appellant directs the reader to the milk specific references. Nevertheless, the Examiner discounts all of the detailed characterization provided by the milk specific references.

For example, the Examiner disposes of Qasaba et al., which has extensive disclosure on the structure of the 5' control regions of a rat and chicken milk specific promoters, because there is allegedly "no guidance on those portions of the 5' flanking region which have promoter activity." What the Examiner is asking for here is a correlation of a specific motif with the promoter region activity. Appellant argues that this functional or fine structure analysis is irrelevant to possession of this type of promoter. This is a promoter which was already known to include elements which in nature give milk specific expression of the protein normally encoded by the gene by the fact that the expression pattern of its protein was known to be milk specific.

With regard to Jones et al., which the Examiner admits has "fine structure mapping of the rat – casein gene, and proposed sites of expression regulatory sequences", is dismissed on the basis that "this is not considered enabling as no such promoter sequences were analyzed for such regulatory activity." Analysis of the particular sites is not relevant to possession. The art taught the promoter region, in part by demonstration of the canonical structures and location. The art also taught that the promoter, in nature, was milk specific. It is indisputable that the art knew that a β- casein gene gives mammary specific expression in nature. The Examiner is in essence admitting the art possessed the promoter region but that it had just not shown the fine structure or what was the smallest part or particular internal motif which confers specificity. The invention just says use the region, the known region, the region which is known to have elements which in the native state give milk specific expression. Moreover, Appellant points out that this reference does, in fact, disclose the presence of a glucocorticoid receptor binding site in the 5' flanking region, and provides a region homologous to a region of the progestrone receptor- binding site. With no more information provided in the WAP references than is provided for β-casein in the Jones reference, the Appellant was able to select a restriction fragment to use as a promoter.

It is critical to keep several facts in mind when considering this rejection. First, these promoters are by definition milk specific promoters—in nature, they control proteins long known to have milk specific expression in their native settings. Thus, they must have within them the sequences the Examiner is interested in. Second, it is indisputable that almost invariably promoters are in the 5' flanking region. Third, the specification teaches the range of size one should be looking at for the promoter. Given this knowledge, additional details about the fine structure, or what was the smallest part or particular internal motif which confers specificity, are not needed to show possession of the promoters.

The Examiner asks for a "complete 5' structure" see, page 7, line 22. The Examiner is conflating a description sufficient to convey possession with a mechanistic explanation of the invention. While admitting that canonical structures have been disclosed, see page 7, line 21, the Examiner argues that there is more to "identifying" a promoter sequence. In a promoter not already known to have the particular desired property in nature, the Examiner's argument might have more weight, but here it does not. The Examiner demands that to be in possession of the promoter the art must disclose "some special structure(s) or sequence that affords them this designation." (In reality, the references do disclose these structures, but the Appellant's position is that even without such a disclosure the references would provide a description of the promoters.) A milk specific promoter can be distinguished from others by its association with and control of a sequence encoding a milk specific protein in the native setting. This together with the structure provided, e.g., cannonical structures, the 5' end of the message, does in fact correlate the desired tissue specificity with the structure disclosed. One can be in possession of something, e.g., a larger sequence, e.g., a promoter region, without a correlation of a particalur internal structure that gives the activity. That is particularly true in this case, the promoters function in nature to give mammary specific expression.

The Examiner's erronious formulation of the problem runs throughout the entire response. At page 8, lines 7-8 the Examiner says "Furthermore, as discussed above the references do not state that they have taught promoter sequences." This is simply incorrect, the references discuss promoter structures in great detail. They do not provide the analysis sought by the Examiner but that analysis is irrelevant to the claims.

At page 8, lines 22-24, the Examiner asserts that "all the references do at most is point to structures and sequences common to all promoters, and not to point to structures that would make the promoter a mammary gland promoter or a milk protein promoter." Those structures, and the structural fact of being linked to the coding sequence of a milk specific protien allow one to identify and distinguish these promoter regions from other DNA, e.g., other promoter regions. Again the Examiner is not focusing on the invention. Indeed, the Examiner here seems to be admitting much if not all of what, in view of the rest of the art and spcification, is needed to provide a written description of the claimed constructs is available.

The Examiner's argument ignores the fact that the proteins expressed under the control of these promoters were known to be expressed in a tissue specific manner, in the mammary tissue in their native setting. Although the milk protein references actually do point to structures and motifs in the promoter region which are involved in mammary gland specific expression, this information is not necessary. The generic or canonical structural information available regarding the promoter regions and the knowledge that these promoters are part of genes which result in milk specific expression in their native setting—is sufficient to demonstrate the possession of milk specific promoters in the art.

In the section which begins at page 9, line 1, the Examiner refers to the Appellant's discussion of the state of the art in mammalian promoters. The Examiner states that "It would also appear that applicant is inserting standards for enablement into written description." This is decididly not the case. As is discussed above, the Guidelines require that the sufficiency of written description

be evaluated in light of the knowledge and skill in the art. Appellant has provided information on the state of knowledge in the art for this reason. In prosecution of the case, and in this appeal, Appellant has discussed two types of references which show the development of the art. The level of skill in the art is shown by the first class of references which disclose DNA fragments which include milk specific promoters argued by the Examiner to not be described and by a second class or group of references which show the high degree of sophistication of the selection of elements and the combining of such elements into a single sequence in a vector. This latter class of references is not provided to in any way to try to focus on enablement and distract the reader from the issue of written description but rather to help place the disclosure of the first group of references in context, to help illustrate what those references and the terms used in the specification would mean to one who read them.

It is against this background of familiarity with the promoters that the sufficiency of the written description of the specification must be judged. As the Examiner correctly remarks a few lines later, the sufficiency of written description includes consideration of "whether or not the skilled artisan would know that applicant ... had possession of the claimed invention for its breadth given the disclosure. (emphasis added). The art cited by the Appellant merely allows one to view the milk specifc promoter art as it would have been viewed by the artisan of ordinary skill.[2] The dozen or so references, including Cilliberto et al., in the second class merely show the knowledge in the art. Appellant argues that the art was in possession of the promoters, and the cited references, together with the milk specific promoter references themselves, show the level of knowledge in the art, in other words demostrate possesssion by the art. This is and has always been the Appellant's argument. The Appellant has not relied on ease or routineness of discovery by one guided by the specification as Appellant argues that the promoters were already in the art.

The Examiner also criticizes these references, see page 9, line 9-line 21, in that they do not reveal the "special features of the milk protein gene promoter". The references were not relied on for this purpose but rather for the purposes discussed just above. The Examiner extends the same misplaced argument applied to the milk promoter references to these references, namely that they "do not establish knowledge of all structures and /or sequences required to make a mammalian promoter." The key word the Examiner uses is "knowledge." As the Examiner uses it, the term is imbued with standards that go far beyond those of written description as applied to the facts of this case. In the Examiner's use, the term requires a level of mechanistic understanding which is not required to be in possession of the promoter. The structural features one needs are the 5' region, the fact that it is in the front of a milk specific gene, or the same or similar, and the rough size of a piece to use. All of that is in the art or the specification.

A key fallacy in the Examiner's argument is shown by the statement on page 9, lines 22-24, "If these structures are not important to the invention, then, any promoter would suffice, and applicant's claim to milk protein promoters really would mean any promoter." The Examiner is apparently overlooking it, but promoters of the invention are limited to promoters derived from

[2] The references referred to here and elsewhere as "promoter art" refers to the references discussed at pages 19-22 of the Appeal Brief.

one of the genes which encodes and expresses a milk specific protein. This is a distinct and limited family and most emphatically not any gene. These milk specific genes (and the promoters) are known by the expression profiles of the proteins they encode. Actual physical inclusion of the structures within the promoters may be important but that is distinct from pointing them out in the sequence which the specificatoin directs should be used. The art teaches the larger structure, which includes the identified canonical elements, and specific or special elements. The fact that the promoter is known, by definition, to show mammary specific expression in nature, tells you that you are in the right promoter. If there is doubt about a particular nucleic acid, it can be tested in the system described in the WAP example in the specification.

The Examiner makes similar arguments on page 9, see lines 11-13, where after again discussing the lack of explicit delineation of the sequence motifs within a promoter which give rise to mammary specific expression, the Examiner concludes that the references "do not teach anything regarding structures that cause the 5' flanking region of a milk protein gene to impart mammary gland specificity or that make a promoter a milk protein promoter rather than an insulin promoter." This is grossly incorrect. The 5' flanking regions disclosed (and in many cases at least partially sequenced) were presented in the context of just such tissue specific expression—they are genes known to express mammary specific proteins. It is not clear what could be a more explicit context of tissue specific expression.

At page 9, lines 21-24, the Examiner again asserts that "no milk protein identifying structural features were either disclosed in the specification nor known in the art at the time of filing."

The Examiner argues that Apellant's milk promoter sequences "were not known at the time of filing." Table 1 (page 14) shows that this is simply not the case. The sequences of the promoter region are there, in the references. They are known to be capable, in their native setting to provide milk specific expression and they are stucturaly identified and cloned in the milk specific promoter references discussed in Table 1. The invention is not disclosed in the art, i.e., the realizaton that milk specific promoters could be used to provide mammary specific expression of a heterologous gene in a transgenic animal. A detailed correlation of the particular sequence motif within the promoter which confers specificity (as opposed to a more generic or canonical element such as a TATA box) is not needed[3]. This mechanistic understanding of how, on a molecular level, the invention works is not needed for the possession of a milk specific promoter. This is not needed to identify or distinguish the milk specific promoters from other promoters. The milk specificity is revealed by the art-known pattern of expression in the native setting. In essence, the inventors found the art in posssion of the milk specific promoters. They discovered a new use for those promoters. The art knew they were there. The inventors showed they could be used to provide mammary specific expression of a heterologous gene in a transgenic animal.

[3] Although not needed, as argued elsewhere herein, the art does provide such information.

The Examiner admits that the WAP promoter meets the written description requirements. The state of knowledge of the WAP promoter does not differ significantly from the art that provides for the other milk specific promoters which the Examiner argues do not meet the requirements. It is difficult to see how WAP could meet the written description while the others do not. Thus, Appellant argues that the Examiner's admission that the WAP promoter meets the statutory requirements amount to an admission that the other promoters are also sufficiently described.

On page 10, first full paragraph, of the Office Action the examiner argues that there is nothing in the Guidelines that the holdings in Amgen, Fiers and University of California are limited to DNA sequence claims. Although Appellant's argument does not rest on this point, Appellant points out that the holding in Amgen was explicitly limited to the invention of genes:

> We hold that when an inventor is unable to envision the detailed constitution of a gene so as to distinguish it from other materials, as well as a method for obtaining it, conception has not been achieved until reduction to practice has occurred, *i.e.*, until after the gene has been isolated. Amgen at 1206 (emphasis added).

The court in Lilly held that:

> A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus. (emphasis added)

One could certainly argue that a requirement for sequence in U.C. v. Lilly was limited to cDNA or perhaps other gene claims.

Once one moves beyond the holding on the specific facts in these cases, and moves to applying the guidance and general principles set out for other fact patterns the picture changes even more. What is clear is that, perhaps even in the narrow area of cDNAs, and beyond a doubt in other areas, the court did not close the door to other methods of meeting the requirement:

> However, it may not be necessary to enumerate a plurality [*28] of species if a genus is sufficiently identified in an application by 'other appropriate language.'" (citations omitted). We will not speculate in what other ways a broad genus of genetic material may be properly described, but it is clear to us, as it was to the district court, that the claimed genera of vertebrate and mammal cDNA are not described by the general language of the '525 patent's written description supported only by the specific nucleotide sequence of rat insulin. (emphasis added)

The Guidelines emphasize the case-by-case nature of the inquiry. The Examiner is attempting to apply the most narrow holding in the line of cases which follow Amgen to a very different set of

claims and a very different invention. In addition, the Examiner ignores or gives little weight to the requirements in the guidelines and, in the very cases relied on for the rejection, that the level of knowledge in the art affects the level of disclosure needed. On page 11, line 25 to page 12, line 1, the Examiner argues 'While Lilly may state other means can be used to describe a DNA sequence other than a base pair order, Lilly did not offer such and the applicant has failed to adequately describe by another means, and name is such a non-adequate means." The case law, primarily Amgen and Lilly, do not state the other "such means" precisely because they did not want to be limiting. **And, the other means, here it is the combination of the identification of canonical elements together with location within the larger structure of a gene which encodes a mammary specific protein. e.g., a casein, lactalbumin or WAP protein.**

The case law, including Amgen, does not use a simple rule for what is needed to provide a sufficient writen desciption. The law uses a standard which tailors the type of description required to the invention. The standard requires distinguishing the invention from other materials. In Amgen, the invention was a new gene, and the court found that application of the standard in that setting required the entire sequence. One must look at the standard and the specific facts. Here the Examiner ignores application of the standard to the particular facts of the case, which facts are very different in terms of what the art knew from that known in the fact pattern in Amgen, and simply jumps to the conclusion of requiring the same answer as in Amgen. The same standard can (and in fact must) give different results when applied to significanly different fact scenarios. There is a means here of distinguishing the milk specific promoters from all other promoters—the art provides that by providing a variety of promoters which are known in nature to give milk specific expression. This distinction can be made without any reference to the specific sequence motif data the Examiner requires. It should also be pointed out that many of the milk specific promoter references discuss the very elements the Examiner argues need to be included, see our arguments elsewhere herein. It needs also to be remembered, that a great deal of structure, including DNA sequence data, is provided by the milk specific promoter art.

Appellant also points out the previously quoted passages from Amgen v. Hoechst and TKT, which emphasize the fact specific nature of each written descritpion inquiry and the importance of the level of skill in the art in evaluating sufficiency of written description. The same case emphasizes the rule that all genetic elements are not subject to the same holding as found in UC v Lilly, and that those cases are "inapposite" to fact situations such as presented in the instant matter:

> More recently, in Enzo Biochem, we clarified that Eli Lilly did not hold that all functional descriptions of genetic material necessarily fail as a matter of law to meet the written description requirement; rather, the requirement may be satisfied if in the knowledge of the art the disclosed function is sufficiently correlated to a particular, known structure. See Enzo Biochem, 296 F.3d at 1324, 63 USPQ2d at 1613. Both Eli Lilly and Enzo Biochem are inapposite to this case because the claim terms at issue here are not new or unknown biological materials that ordinarily skilled artisans would easily

miscomprehend.[4] Instead, the claims of Amgen's patents refer to types of cells that can be used to produce recombinant human EPO. Amgen v. Hoechst and TKT, 314 F.3d at 1332.

On page 10, lines 19-22, the Examiner argues, " With respect to Amgen, while it is true that the 5' flanking regions for alpha-lactalbumin, alpha-casein, beta-casein, and gamma-casein were known in the art at the time of filing, the relevant structure or sequence that makes these regions specific for expression of WAP, lactalbumin, lactoglobulin, or casein were not known, were not taught in the cited references and not disclosed in the specification." There are several flaws in this argument. First, the Examiner again demands a description of elements that are not claimed and that are not needed to describe the invention. In addition, the Examiner admits that the 5' flanking structures were known. This is a key admission, since together with the details of canonical structure provided in the same references, the knowledge that they were part of a gene which results in nature with milk specific expression and the disclosure of the application, it provides a written description of the disputed claim limitation. Finally, and though the Appellant's argument in no way depends on this, the references to appear to describe the elements the Examiner requires.

At page 11, lines 1-24 of the Office Action, the Examiner discusses the nature of the genus. The Examiner argues that the choice of genus by the inventors was arbitrary. That highly conclusory statement is not supported with any factual analysis as to why the genus is arbitrary. The discussion provided above has elucidated a number of common structural and functional properties, which suggests that the choice was anything but arbitrary. The Examiner has also failed to provide arguement as to why an arbitrarily choosen genus is not acceptable. The inventors choose that formuation for a genus and the Appellant is unaware any reason why they should not be able to do so. Rather than attack the inventors' formulation as arbitrary, the better view would probably to see it as a genus which includes both subgenera and species. Regardless of the ability to construct sub-generic structures beneath the genus selected by the inventors, the Appellant has described sufficient individual species to describe the genus. As is discussed above, representatives of the large majority of the species, in the sense of type of promoter, were known in the art. In addition, milk specific promoters from at least three species have been described in the art, see the milk specific promoter references.[5] As is discussed extensively herein, given the nature of the promoters required in the claims, the genus is sufficiently described.

---

[4] Indeed, Amgen's patents appear to satisfy the sequence requirement in Eli Lilly insofar as Figure 6 of the patents expressly discloses the complete (albeit slightly incorrect) sequence of human genomic EPO DNA and the encoded DNA.

[5] As used herein, the milk specific promoter art, or milk specific promoter references, refers to the references which disclose and analyse the promoters of genes known to show, in their native state, milk specific expression, which references were discussed above at pages 14-18. These references include: Qasaba and Safaya (1984) Nature 308:377-380; Campbell et al. (1984) Nucl. Acids Res 12:8685-8697; Yu-Lee et al. (1986) Nucleic Acids Res.14:1883-1902; Stewart et al. (1984) Nucleic Acids Res.12:3895-3907; Jones et al. (1985) J Biol Chem 260:7042-7050; and Yu-Lee and Rosen (1983) J Biol Chem 258:10794.

The Examiner's argument, see page 11, lines 6-10, seems to rely a great deal on specific promoters being patentable over one another as a way of attacking the Appellant's genus. Appellant is not aware of any support for the proposition that patentability of one species over another would negate the genus. One could certainly envision a situation where enough common properties were known to have a genus but there were sufficient differences to allow patentability of narrow claims to one promoter over another similar but not identical structure.

At the end of the passage under discussion, the Examiner says that other than the 5' flanking location and the cannonical structures it is not clear how the promoters are structurally similar. By saying this the Examiner admits the existance of sufficient structure—namely the existance and location of canonical structures (which informs one that he or she is in possession of a promoter sequence) and a location in the 5' structure of a gene which encodes a milk specific protein (which informs one that he or she is in possessioin of a milk specific promoter)—sufficient to put one in possession of the invention, in other words to distinguish it from other promoters,namely promoters that are not a structural element of a gene having a coding region of a milk specific protein.

Again, at page 11, lines 12-15, the Examiner argues that "further, the fact that the number of milk protein promoters is not relevant given that they are of a different sequence, and the sequences or structures that make them milk protein promoter, or a specific milk protein promoter is not known." The small number is relevant in two ways. First, by small number is meant not only the absolute number but also the fact that the number is severly limited by the fact that the only promoter regions in the genus are those dervied from the limited number of genes which encode milk specfic proteins. The fact that a large number of the different milk proteins, genes and promoters were known for five of the seven members of this genus is relevant. In addition, several of these proteins, genes and promoters had been identified for several species.

The Examiner concludes the section on written description as follows:

> In summary, the holdings of Amgen, Fiers and Lilly is quite appropriate and are part of the Written Description Guidelines. Further, the holdings in court decisions are frequently applied broadly to cases with different fact patterns. If this were not the case, then the holdings of In re Wands would only apply to cases where monoclonal antibodies were made. The essence here is structure, as opposed to absolute sequence. However, when the discussion includes promoter sequences, DNA sequence is at least part of the total equation as it provides the structure. Thus, as the cited case law discusses DNA sequences in terms of structure, they are clearly applicable to more than novel genes. Thus, as stated above, absent teachings either in the art at the time of filing of the specification of structures in the 5' flanking sequences of the α-lactalbumin, α-casein, β-casein and γ-casein genes that makes mammary gland specific or make promoters behave as expression regulatory sequences, the claims lack written description for their entire breadth.

Appellant agrees that the holdings of Amgen, Fiers and Lilly are relevant to understanding the standards to apply for written description and the Written Decription Guidelines. However, the Examiner's rationale for broadly requiring the same outcome found in the narrow holdings of these cases to the very different fact pattern of the instant matter is flawed. The Examiner argues that the "holdings in court decisions are frequently applied broadly to cases with different fact patterns ...[i]f this were not the case then the holdings of In re Wands would only apply to cases where monoclonal antibodies were made." This rationale is simply incorrect—the standards set forth in In re Wands to evaluate undue experimentation may be used broadly—but that standard, depending on the specific fact patterns at hand, can give very different results. It often gives the opposite outcome from that in the original case. The holding of In re Wands, that undue experimentation was not required to obtain the claimed monoclonal antibodies, depended on the specific facts set forth in that case and is clearly not applied broadly across every technology. Instead—the standard set forth by In re Wands is broadly used by courts to analyze the particular facts at hand.

Similarly, the case law regarding written description, including Amgen, does not use a simple rule for what is needed to provide a sufficient writen desciption. The law uses a standard which tailors the type of description requried to the invention. The standard requires distinguishing the invention from other materials. In Amgen, the invention was a new gene, and the court found that application of the standard in that setting required the entire sequence. One must look at the standard and the specific facts. Here the Examiner ignores application of the standard to the particular facts of the case, which facts are very different in terms of what the art knew from that known in the fact pattern in Amgen, and arrives at the conclusion of requiring the same answer (i.e., the same holding) as in Amgen. The same standard can (and in fact must) give different results when applied to significanly different fact scenarios.

The Examiner oversimplifies the facts presented herein by arguing that (according to the argument) since part of the invention is a promoter, "DNA sequences is at least part of the total equation". Although Appellant agrees that the physical structure is essential, the correlation of specific motifs within the claimed sequence is not essential. While DNA is certainly part of the equation, there is no requirement in the case law that every element composed of nucleotides be treated like the novel genes of Amgen. Indeed, the requirement of the case law, as explained in all of the cases, e.g., in Amgen v. Hoechst and TKT, is a fact-oriented case-by-case analysis which lacks hard and fast automatic rules, even when DNA is concerned. The situation here, where the promoter region is well described, though clearly not in the specific way the Examiner would like, is certainly a very different set of facts from Amgen. Almost the only thing in common between the two fact patterns is that DNA is involved. The specific motif postulated to exist by the Examiner is not claimed. That level of knowledge is simply not needed to describe this invention, as opposed to new gene claims.

As discussed above, the Examiner admits that the canonical structures TATA and CAAT were landmarks for promoters. The milk specific promoter art is replete with disclosure of these canonical structures. Thus, once one had a milk specifc gene one could identify the promoter region. This must be taken together with the fact that milk specific promoters have one other

very critical common structural property, namely that they are part of genes that encode proteins that are known to be milk specific. Thus, the art, which gave very detailed structural analysis of the promoter regions, was sufficiently developed that simply naming them was sufficient to identify them and to be able to tell them form other promoter regions. This information provides the ability to distinguish the milk specific promoters from other types of promoters. The Examiner seeks this result through her requirement of identifying a special milk specific motif. The same result, the ability to distingiush the promoters from other promoters, is provided in a different way by the specification. The Examiner has admitted to every thing else needed for possession. Once one realizes that the promoter region was known, because of its demonstrated and known expression properties, to have the elements needed to give native milk specfic expression, the need for the identification of the special sequence is no longer needed to distinguish the promoters from other promoters. One is left with no conclusion other than that the art had possession of the promoters.

The brief fee of $160 is enclosed. Please apply any other charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

Date: 3/21/03

Laurie Lawrence, Reg 46,593
for Louis Myers
Reg. No. 35,965

Fish & Richardson P.C.
225 Franklin Street
Boston, Massachusetts 02110-2804
Telephone: (617) 542-5070
Facsimile: (617) 542-8906

20526311.doc

Appendix of Claims

1. A DNA construct comprising a gene encoding a protein, said gene being under transcriptional control of a mammalian milk protein promoter sequence which does not naturally control transcription of said gene, said DNA construct further comprising DNA encoding a peptide enabling secretion of said protein.

2. The DNA sequence of claim 1, wherein said secretion enabling peptide comprises a secretion signal peptide which is cleaved from said secretion protein.

5. The DNA sequence of claim 1 wherein said signal encoding sequence is the signal encoding sequence naturally associated with said gene encoding said protein.

6. The DNA sequence of claim 1 wherein said signal encoding sequence is the signal encoding sequence naturally associated with said mammalian milk protein promoter.

7. The DNA sequence of claim 1 wherein said DNA sequence includes a transcriptional stop sequence.

8. The DNA sequence of claim 7 wherein said stop sequence is derived from SV40 virus DNA.

9. The DNA sequence of claim 7, wherein said stop sequence is contained in the polyadenylation sequence of SV40.

11. The DNA sequence of claim 1 wherein said gene encodes human tissue plasminogen activator or hepatitis B surface antigen.

16. The DNA construct of claim 1 wherein said milk protein is a milk serum protein.

17. The DNA construct of claim 16, wherein said milk serum protein is α-lactalbumin.

19. A DNA construct containing a gene encoding a protein, said gene being under the transcriptional control of a sequence upstream from the transcriptional start site of a mammalian milk protein which includes a milk protein promoter and which does not naturally control the transcription of said gene, said DNA sequence further comprising DNA encoding a peptide enabling secretion of said protein.

20. The DNA construct of claim 19, wherein said secretion-enabling DNA comprises a secretion signal-encoding sequence interposed between said gene and said promoter.

21. The DNA construct of claim 19, wherein said milk protein is a milk serum protein.

22. The DNA construct of claim 21, wherein said milk serum protein is α-lactalbumin.

24. The DNA construct of claim 20, wherein said signal encoding sequence is the signal encoding sequence naturally associated with said gene encoding said protein.

25. The DNA sequence of claim 20, wherein said signal encoding sequence is the signal encoding sequence naturally associated with said mammalian milk protein promoter.

26. The DNA sequence of claim 16, wherein said DNA sequence includes a transcriptional stop sequence.

27. The DNA sequence of claim 26 wherein said stop sequence is derived from SV40 virus DNA.

28. The DNA sequence of claim 27 wherein said stop sequence is contained in the polyadenylation sequence of SV40.

29. The DNA sequence of claim 19 wherein said protein is human tissue plasminogen activator or hepatitis B surface antigen.